FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE (PADAC)

Thursday, June 11, 2015

8:02 a.m. to 3:31 p.m.

Hilton Washington DC North/Gaithersburg

620 Perry Parkway

Gaithersburg, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:02 a.m.)

Call to Order

Introduction of Committee

DR. SWENSON: I would like to remind everyone please to silence your cell phones or other electronic devices, if you have not already done so. And I would also like to identify the FDA press contact, Eric Pahon. If you are present, Mr. Pahon, could you stand? Thank you very much.

My name is Erik Swenson. I'm the acting chairperson for this meeting of the Pulmonary-Allergy Drugs Advisory Committee. I will now call this meeting to order, and I'd like to start by going around the table and having all the members of the FDA and the advisory panel introduce themselves, and we'll start with Dr. Albrecht.

DR. ALBRECHT: My name is Helmut Albrecht. I'm the acting industry representative on this panel, and I work for H2A Associates, LLC, which is a pharmaceutical consulting firm. I also have a management position at Alitair Pharmaceuticals,

which is a small startup developing bronchiectasis drugs in the U.S.

DR. RAGHU: I'm Ganesh Raghu from the University of Washington Medical Center in Seattle. I'm a pulmonologist and director of the Center for Interstitial Lung Disease at the University of Washington in Seattle.

DR. DYKEWICZ: I'm Mark Dykewicz. I am chief of allergy and immunology and professor of medicine at St. Louis University School of Medicine, St. Louis.

DR. EVANS: I'm Scott Evans. I am a pulmonologist at the University of Texas MD Anderson Cancer Center.

MS. SCHWARTZOTT: I'm Jennifer Schwartzott. I'm the patient representative for this meeting and a lifelong asthma sufferer. S

MS. BELL-PERKINS: Hi. Elizabeth Bell-Persons. I'm acting consumer rep for this meeting.

DR. AU: I'm David Au. I'm a pulmonologist at the VA Puget Sound Health Care System in

Seattle, Washington, and health services researcher.

DR. FOLLMANN: I'm Dean Follmann, head of biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. STONE: Kelly Stone. I'm deputy chief, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases.

DR. GEORAS: Hi. I'm Steve Georas, pulmonary critical care physician at the University of Rochester in New York. I have been studying eosinophilic inflammation for many years, and I also direct the Severe Asthma Clinic.

DR. SWENSON: Erik Swenson. I'm at the Seattle Veterans' Affairs Medical Center, and I'm a pulmonologist and do critical care medicine.

DR. TOLIVER: Kristina Toliver, acting DFO.

DR. MORRATO: Good morning. Elaine Morrato. I'm an epidemiologist, and I'm the dean for public health practice for the Colorado School of Public Health.

DR. CONNETT: John Connett. I'm in

biostatistics at the University of Minnesota.

DR. BLAKE: Kathryn Blake. I'm a research pharmacist in the Center for Pharmacogenomics and Translational Research at Nemours Children's Specialty Care in Jacksonville, Florida.

DR. CARVALHO: Good morning. I'm Paula Carvalho. I do pulmonary critical care. I'm with the Boise VA, and I'm with the University of Washington. Thank you.

DR. ABUGOV: Robert Abugov. I'm the statistical reviewer for the FDA for this submission.

DR. CHAUDHRY: Sofia Chaudhry, clinical reviewer, Pulmonary Allergy, and Rheumatology Products, FDA.

DR. GILBERT-McCLAIN: Lydia Gilbert-McClain, deputy director, Division of Pulmonary, Allergy, and Rheumatology Products, FDA.

DR. CHOWDHURY: I'm Badrul Chowdhury. I'm the division director, same division.

DR. SWENSON: Thank you, everyone.

For topics such as being discussed today at

today's meeting, there are often a variety of opinions, some of which are held quite strongly. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I'll pass on the mic to Dr. Kristina Toliver, who will read the Conflict of Interest statement.

Conflict of Interest Statement

DR. TOLIVER: The Food and Drug Administration is convening today's meeting of the Pulmonary-Allergy Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972.

With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with Federal ethics and conflict of interest laws, covered by but not limited to those found at 18 USC Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and

temporary voting members of this committee are in compliance with Federal ethics and conflict of interest laws under 18 USC Section 208. Congress has authorized FDA to grant waivers to special U.S. Government employees and regular Federal employees who have potential financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 USC Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves a discussion of the biologics license application 125526 for

mepolizumab for injection, submitted by GlaxoSmithKline for the proposed indication of add-on maintenance treatment in patients 12 years and older with severe eosinophilic asthma identified by blood eosinophils greater than or equal to 150 cells/microliter at initiation of treatment or blood eosinophils greater than or equal to 300 cells/microliter in the past 12 months.

This is a particular matters meeting during which specific matters related to GlaxoSmithKline's mepolizumab for injection will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry

representative, we would like to disclose that Dr. Helmut Albrecht is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Albrecht's role in this meeting is to represent industry in general and not any particular company. Dr. Albrecht is employed by H2A Associates.

We would like to remind members and temporary voting members that if the discussion involves any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. SWENSON: Thank you, Dr. Toliver.

We will now proceed with the FDA opening remarks and presentation from Dr. Lydia

Gilbert-McClain. I would like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Dr. Gilbert-McClain?

FDA Opening Remarks and Regulatory History

DR. GILBERT-McCLAIN: Thank you, Dr. Swenson.

Good morning. My name is Lydia Gilbert-McClain and, again, I'm the deputy director in the Division of Pulmonary, Allergy, and Rheumatology Products at the FDA. And on behalf of the FDA, I would like to welcome the advisory committee members to this meeting.

As members of the FDA Advisory Committee, we consider your expert scientific advice and recommendations an important component to our regulatory decision-making processes. I want to thank you for your preparation in advance of this meeting and your attendance here today, and we look forward to the discussions and feedback that you

will provide. I want to thank the chair, Dr. Swenson, for presiding over today's meeting.

The objective of today's meeting is to discuss the new biologics licensing application submitted by GlaxoSmithKline for mepolizumab for subcutaneous injection once every 4 weeks in the treatment of severe asthma.

Along with the overall discussion of the efficacy and safety of mepolizumab, other issues for consideration for which we are seeking input from the committee include additional feedback on the patient population most likely to benefit from treatment with mepolizumab and, in particular, the role of blood eosinophil levels in determining initiation of treatment with mepolizumab; secondly, the adequacy of the data in the pediatric and adolescent population 12 to 17 years of age; and finally, the adequacy of the data in the minority population and, in particular, African-Americans.

Mepolizumab for injection is a humanized monoclonal antibody to interleukin 5. Mepolizumab acts by preventing interleukin 5 from binding to

its target receptor complex on the eosinophil cell surface, resulting in decreased peripheral blood and tissue eosinophils. The proposed dose and route of administration is 100 milligrams by subcutaneous injection once every 4 weeks, administered by a healthcare professional.

Mepolizumab is not currently marketed in the U.S. or any other country in the world and, if approved, would be the first monoclonal antibody to interleukin 5 to be approved for any indication and will represent just the second monoclonal antibody product to be approved for an asthma indication, omalizumab, an anti-IgE monoclonal antibody, being the first.

The target population for this therapy is a severe asthma population. You will note that the verbatim indication statement that was cited in our briefing documents and in the Federal Register notice for this advisory committee meeting is not shown here on this slide. This is because the exact wording of the indication statement, should this product be ultimately approved, will be worked

out later between the agency and GSK. We are interested today in your input of the concept to be captured in the indication statement and not the exact wording.

The agency acknowledges that mepolizumab, if approved, should be directed to a targeted patient population with severe asthma with a history of exacerbations in spite of maximum controlled therapy as an add-on to maintenance therapies. Furthermore, given the mechanism of action of mepolizumab, it is anticipated that blood eosinophil levels will play a role in directing therapy. The proposed age for the target population is 12 years of age and older.

Despite having several products approved for the long-term maintenance treatment of asthma, therapeutic challenges remain in the management of severe asthma. It is estimated that about 5 percent of the asthma population have severe uncontrolled asthma despite being on maximum therapy, and many of these patients are on oral corticosteroids and are still uncontrolled.

Patients with severe uncontrolled asthma are more likely to experience frequent asthma exacerbations, including hospitalizations. Therefore, development of safe and effective asthma therapies targeted to this subpopulation would be an important therapeutic step in improving clinical outcomes in this chronic lung disorder.

Shown here on this slide is a graphic representation of the mepolizumab development program from the initial trial completion in 1999 up to the current time with the completed pivotal studies in the subpopulation of severe asthmatics and the submission of the application. You will see this graphic again in the FDA presentation, and our clinical reviewer, Dr. Sofia Chaudhry, will expand on this further. However, I would like to highlight a couple of points.

First, you will readily note that there is a considerable gap in clinical trial activity from the completion of the first trial, study 06, to the conduct of the clinical development program in severe asthma patients. Between those time points

are two investigator-conducted studies that provided information that GSK used to guide the design of the pivotal studies in the severe asthma population.

Secondly, the selection of exacerbation rate in two of the studies, studies 88 and 97, and the selection of oral corticosteroid reduction in one study, study 97, as primary endpoints in the severe asthma program is a departure from the usual asthma programs that encompass the full spectrum of asthma where lung function, and specifically FEV1, is typically the primary endpoint.

The agency acknowledges asthma exacerbation as a robust and clinically relevant outcome such that demonstration of efficacy using exacerbation as a primary endpoint in a severe asthma population would be appropriate.

Given the morbidity associated with frequent asthma exacerbations, a significant reduction in this clinical outcome would on its own merit represent a clinically meaningful improvement in the lives of severe asthma patients.

GSK evaluated both the intravenous and the subcutaneous routes of administration in the development program, and the first clinical study, study 06, was conducted with a pilot formulation of mepolizumab using intravenous dosing. Subsequent dose ranging and efficacy studies were conducted with a mepolizumab product that is of a higher concentration than the product proposed for marketing, but the formulation is otherwise the same and there is adequate chemistry and manufacturing, bridging data to support the to-be-marketed product, which is currently being used in the open-label extension studies 61 and 66.

The data obtained from the clinical studies 97, 88 and 75, along with pharmacodynamic data, appear to be adequate to support the 100-milligram subcutaneous dose proposed for marketing, and the 75-milligram intravenous dose provides similar efficacy to the 100 subcutaneous dose, which is some background information that you should keep in mind as you see the data from both intravenous and subcutaneous routes being presented

to you today.

Finally, note that while the chemistry and manufacturing aspects of drug development are a critical component of regulatory decision-making, the chemistry and manufacturing aspects of the program are not the focus of today's meeting. Today's meeting is only to address the clinical safety and efficacy of mepolizumab.

So here are the issues for consideration presented on this slide. As you listen to the presentations and discuss the data, we would like you to keep in mind this issue of the patient population most likely to benefit from this therapy.

Given the mechanism of action of mepolizumab, it is reasonable to consider blood eosinophils in the selection criteria for initiating therapy. We would like your input on how best this could be accomplished as we consider appropriate labeling language should this product be approved.

While we are not asking you to provide

specific labeling language, we are interested in hearing your perspectives and considerations of this issue, keeping in mind that in the clinical setting, providers will need to exercise a balanced approach of not withholding therapy from patients most likely to benefit, while at the same time, given the heterogeneity of severe asthma, avoid prescribing therapy to patients unlikely to benefit.

Secondly, the limited database in the pediatric population is another issue for discussion. As I mentioned earlier, the proposed indication is for patients 12 years of age and older, but as you will see in the presentations, the data in this age group are very limited.

Thirdly, minority representation, and specifically African-Americans, is another issue for discussion. In general, historically, African-American representation in asthma programs has been low. However, the representation of the African-American population is even smaller in this program.

This limited data in African-Americans is of concern particularly since this product is specifically targeted to a severe uncontrolled asthma population. Given the increased asthma morbidity and mortality reported in asthmatic patients of African-American descent, representation of African-Americans in any severe asthma development program would be of particular interest.

So as you listen to the presentations this morning, we ask that you keep these issues in mind. Later today, you will be asked a series of questions. There will be two discussion questions and three voting questions, and you will see that the voting questions will be split out into adult and pediatric populations.

Later this afternoon, I will come back to the podium and go over these questions in more detail when I give the charge to the committee.

So again, I would like to thank you for your time and your attention here today. I will now turn the microphone back to the chair, Dr. Swenson,

to continue the meeting. Thank you.

DR. SWENSON: Thank you, Dr. Gilbert-McClain.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's nonemployee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest and those based upon the outcome of the meeting.

Likewise, FDA encourages you, at the beginning of your presentation, to advise the committee if you do not have any such financial relationships. If you choose not to address this

issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the GlaxoSmithKline presentation, and I hand the podium over to Mr. Yancey, the development leader at GlaxoSmithKline.

Applicant Presentation - Steven Yancey

MR. YANCEY: Thank you, Dr. Swenson, and good morning. I can assume that you can hear me, because I'm going to acknowledge now the audio can be challenging at times, from our viewpoint. So if there is a problem, I would appreciate acknowledgment of that.

My name is Steve Yancey, and I am the medicine development leader for mepolizumab. On behalf of GlaxoSmithKline, I would like to thank the agency and the committee for this opportunity to review the benefit and risk profile of mepolizumab in patients with severe asthma and eosinophilic inflammation. As you can see on this slide, the proposed trade name for mepolizumab is

Nucala.

Today we will critically review the benefit/risk profile of mepolizumab. Mepolizumab is a first-in-class anti-IL5 antibody that reduces airway eosinophilic inflammation. By reducing eosinophilic inflammation, treatment with mepolizumab will reduce exacerbations in a group of patients who experience frequent exacerbations.

Mepolizumab improves lung function and quality of life and also is an effective agent to reduce daily oral prednisone. By utilizing a blood biomarker, the medicine is targeted only to patients likely to respond to treatment. Thus, mepolizumab represents an advance in personalized medicine.

Any new treatment should be well tolerated and the safety profile of mepolizumab is similar to the safety profile in patients receiving placebo added to standard of care.

In a moment, I'm going to hand off to Dr. Pavord, who will describe the life experience of patients with severe asthma. But first, let me

say a few words about how mepolizumab can alter the pathology of eosinophilic inflammation and also summarize the development program.

The role of the eosinophil is widely recognized. Recent studies have shown that increased numbers and activation of eosinophils in the airways of patients with severe asthma is common.

The eosinophil contains diverse preformed cytotoxic mediators. Activating stimuli can lead to the release of these mediators in the lung, and this leads to airway inflammation, which contributes to poor asthma control and exacerbations. Thus, reducing eosinophilic airway inflammation is a rational therapeutic approach in patients with severe asthma.

In order to control eosinophilic inflammation, we must first understand what regulates eosinophil function. Eosinophil function is primarily regulated by the cytokine interleukin 5 or IL5. IL5 plays a key role in the growth, differentiation, mobilization, trafficking,

recruitment, and survival of eosinophils.

The over-expression of IL5 results in a marked increase in blood and lung eosinophil numbers, which increases the total levels of released cytotoxic inflammatory mediators and, in turn, results in exacerbations.

Shown there on the bottom-middle of the slide is the protein structure for the humanized monoclonal antibody, mepolizumab. Mepolizumab is engineered to bind to a specific protein amino acid sequence found only on IL5. By binding to IL5, mepolizumab neutralizes the ability of IL5 to up-regulate eosinophils.

Thus, by inhibiting the regulatory function of IL5, mepolizumab decreases blood and lung eosinophil numbers, which reduces the total levels of released inflammatory mediators, which, in turn, reduces the exacerbation events and improves quality of life.

Now, I would like to briefly review the clinical program for mepolizumab. This slide depicts the nine studies included in the phase 2

and phase 3 program. For convention, we will refer to each study by only the last three numbers of each study identifier.

The clinical development program can be divided into three stages. The early phase 2 studies are shown in blue, the pivotal phase 3 program is shown in orange, and the open-label studies are shown in yellow.

The phase 2 studies included patients across a range of asthma severities. For example, study 006 enrolled patients with moderate asthma who were not selected based upon airway eosinophilia and limited efficacy was demonstrated.

However, in subsequent proof-of-concept studies, when patients with severe asthma are selected based on evidence of airway eosinophilia, mepolizumab was shown to be an effective medicine to reduce exacerbations and also reduce the need for daily prednisone. In addition, data from study 092 characterized the pharmacological dose response to mepolizumab.

The second developmental stage included

three phase 3 studies. Exacerbation study 997 was a 52-week dose-ranging study with IV doses of mepolizumab and confirmed the IV dose to take further into phase 3.

The study also informed on the clinical and blood biomarkers, which identify a patient likely to respond to mepolizumab. The process for identifying the blood biomarker will be reviewed in detail during our presentation of efficacy.

The second large exacerbation study, 588, was the first study to select patients based exclusively on the clinical and blood biomarkers, which were derived from study 997. This was also the first study to include subcutaneous dosing.

Steroid-sparing study 575 was the second study to target patients using the clinical and blood biomarkers derived from study 997, and this study included only subcutaneous dosing.

In the third stage of the program, there are two open-label extension studies. The open-label studies provide long-term safety data for mepolizumab administered subcutaneously for up to

three years in some patients.

Prior to reviewing the full breadth of data described in the efficacy and safety profile of mepolizumab, I would like to preview the proposed indication statement, which we believe is well supported by the clinical data.

The proposed draft indication statement was submitted to the agency as a framework for discussion and includes characteristics of patients who may benefit from treatment with mepolizumab.

There are a few key points worth noting. First, Nucala should be used as an add-on therapy. This means that Nucala should be added on top of high-dose inhaled corticosteroids plus at least one additional controller.

Second, Nucala is intended for patients based on a biomarker of blood eosinophils greater than or equal to 150 cells per microliter at the initiation of treatment or greater than 300 cells per microliter in the last 12 months. And lastly, Nucala has been shown to reduce exacerbations in patients with a history of exacerbations.

Nucala will be supplied as a dry powder in a vial ready for reconstitution and administration by a healthcare professional. The recommended dose is 100 milligrams administered every 4 weeks in the upper arm, thigh, or abdomen.

Lastly, on this slide is the agenda for the key clinical presentations. We have one of the program external advisors with us today. Dr. Ian Pavord is a professor of respiratory medicine at the University of Oxford in the U.K. He is a practicing respiratory physician and specializes in the study and care of adolescent and adult patients with severe asthma.

He will describe the life experience of patients with severe asthma, and he will also describe his experience as a clinical investigator with mepolizumab.

Then Dr. Hector Ortega, the lead physician for the mepolizumab development program, will present the efficacy results.

Dr. Robert Leadbetter, the lead physician in GSK's safety group, will present the safety

profile; and following Dr. Leadbetter's presentation, I will return to the podium with closing comments, and we will happy to take any clarifying questions.

I will now turn the podium over to Dr. Pavord.

Applicant Presentation - Ian Pavord

DR. PAVORD: Thank you, Steve. And thank you to the agency for giving me this opportunity. My name is Ian Pavord. I'm professor of respiratory medicine at the University of Oxford, and I've been interested in severe asthma as a condition and a clinical researcher for 20 years.

I have some relevant conflicts of interest, which I'd like to disclose. Firstly, I've been paid honoraria and speaker fees and expenses by GSK. Secondly, the institution, I worked and received an unrestricted grant for an investigator-lead early clinical trial of mepolizumab in severe eosinophilic asthma, which I will tell you about, but I have no GSK shares or shares in any other pharmaceutical company.

Now, I'm going to talk today about an important group of patients with severe asthma, and these are patients who require a lot of treatment to control their disease or whose disease remains uncontrolled despite a lot of treatment. And I really mean maximum doses of inhaled steroid, usually with one or two additional controllers, commonly a long-acting beta agonists. And some of these patients may require long-term regular oral corticosteroids or omalizumab for their condition.

This is a small fraction of the total asthma population. Shown here is the 24.6 million Americans with asthma. And you will see that 5 to 10 percent of this population have severe asthma, as I've just defined it, and about half of those have severe refractory asthma, meaning that they have persistent symptoms and/or exacerbations.

Of that population, up to 60 percent have eosinophilic disease and might potentially be candidates for treatment with mepolizumab. Now, this is a small proportion of the total asthma population, but it's important, and they account

for just over half of total healthcare direct costs attributable to asthma.

The best definition of severe asthma is that provided by the Joint European Respiratory Society and American Thoracic Society guideline group, who reported last year in the European Respiratory Journal.

They suggest that severe asthma is asthma which requires a treatment with high-dose inhaled steroids and long-acting beta agonists; or leukotriene modifiers; or theophylline for the previous year; or systemic corticosteroids for at least half of the previous year to prevent it from becoming uncontrolled; or asthma which remains uncontrolled despite this therapy.

One important aspect of the guidelines is that they set out different criteria for poor control, and at no point do they suggest that these are related criteria, so they are mutually exclusive. So a patient may have uncontrolled asthma because of persistent symptoms commonly quantified using simple questionnaires such as the

ACQ or the ACT.

They may have severe asthma because of frequent severe exacerbations, and the guideline group suggests two or more bursts of systemic corticosteroids lasting at least three days in the previous year; or that may have had a severe asthma attack resulting in hospital admission, intensive care stay, or even mechanical ventilation.

Asthma can be uncontrolled if lung function is impaired, defined as a pre-bronchodilator FEV1 of less than 80 percent of predicted in the setting of airflow obstruction. And asthma which worsens on tapering high intensity treatment could also be regarded as uncontrolled.

Now, in my talk, I'm really going to focus mainly on exacerbations. And my justification for doing this, well, firstly, this is the clinically most important aspect of the disease. Asthma exacerbations can be catastrophic.

You will recognize the actress shown on the right of this picture from the film *Four Weddings and a Funeral*. Her asthma attack resulted in death

at the age of 33.

These are common episodes. At least half of patients with severe asthma will have had one urgent care visit or more in the year prior to being seen in clinic and at least half will have had at least three courses of oral corticosteroids.

Significant numbers of these patients will have had near fatal events in the past, events that require assessment in the intensive care and mechanical ventilation. These are very disruptive to the patient and result in time off work or time off school.

So this is clinically the most important manifestation of the disease.

Secondly, this is the aspect of the disease that patients fear most. These are episodes of asthma which they have control over. They have to phone for help. These happen at inconvenient times.

This is a simple survey asking a population of patients to rate the aspect of the disease that they would most like dealt with, and less

exacerbations was the top-ranked item, identified by just under 60 percent of the population. So this is a clinically important aspect of the disease which bothers patients the most.

Finally, this is a costly aspect of disease. Shown here are the unadjusted, on the left, and the adjusted total and asthma-related costs broken down by whether the patient has had an exacerbation in the preceding year, shown in blue here. And you will see that costs of moderate and severe asthma are significant, and they are apt to double in a patient that has had a prior exacerbation.

So there is something here. For the clinician, this is a clinically important aspect of disease. It's an aspect of the disease that bothers patients the most, and it's costly.

One other aspect of severe asthma, which I'd like to briefly discuss, is the burden associated with oral corticosteroids either used to treat an exacerbation or used long-term in an attempt to prevent exacerbations.

Long-term oral steroid use is required in

30 to 40 percent of the patient population I'm talking about, and side effects are common. This is the most common cause of drug-related complications.

Side effects show a dose-response relationship, and this dose-response relationship occurs across the dose range that we commonly use to treat asthma, 10 to 15 milligrams a day, and these side effects are costly. And some of them have the potential to permanently harm the patient. So I particularly highlight vertical fractures and myocardial infarctions.

Just to illustrate the sort of impact that severe eosinophilic asthma can have, I'd like to tell you about a patient of mine. She is a 28-year-old bank worker with three young children or preschool children, so she had a tough schedule at home. She presented to me with a six-year history of persistent rinosinusitis and a prior history of surgery for nasal polyposis, very common reported in patients with this pattern of disease.

For three years prior to her assessment, she

had had increasingly severe bouts of wheeze, breathlessness, and cough. And in the year leading up to her assessment, had had these episodes almost monthly and had been hospitalized on three occasions with severe symptoms, and on one occasion nearly died from acute severe asthma and required monitoring on intensive care.

She was non-atopic, as many of these patients are, and had ample evidence of active eosinophilic airway inflammation in the form of a raised exhaled nitric oxide, or FeNO. The normal should be less than 25. Hers was a 155. And the persistent blood eosinophilia at its highest, 1,400 cells per microliter. She had objective evidence of asthma in the form of partly reversible airflow obstruction.

I managed to achieve some stability on the British Thoracic Society step 5 treatment, so NIH step 6 treatment, with regular oral steroids, as well as high-dose Symbicort, daily montelukast. But the prednisolone doses she required to control her disease were between 20 and 30 milligrams a

day, and they had a devastating impact on her.

So she gained 70 pounds in weight. She became depressed. She had significant sleep disturbance and menstrual disturbance. She found it very difficult to cope with the children and her job, and in fact was unable to work as a result of the severe asthma and the treatment required.

My understanding of severe asthma was helped massively by adopting a new technique to assess airway inflammation noninvasively. I was very fortunate in the early '90s to work with Freddy Hargreave in Canada and learned about induced sputum as a method for noninvasively assessing airway inflammation.

You can see at the bottom left an induced sputum cytospin showing evidence of eosinophilic airway inflammation. And this technique proved to be surprisingly robust and applicable in most patients with severe airways disease and safe. And it was particularly good at discriminating the two major patterns of airway inflammation we see, eosinophilic and neutrophilic airway inflammation.

When we started applying this technique to patients seen in the severe asthma clinic, we were very surprised by the findings, and I illustrate the findings with two cases. At the top of this slide, you will see the patient's diary card where they daily quantified their symptoms on a naught to 3 scale, 3 being bad; measured peak expiratory flow; and, the number of times that they required their rescue beta agonist. And at the bottom, you can see their induced sputum cytospin.

So the patient on the left has chaotic and poorly controlled asthma with lots of day and nighttime symptoms, very high beta-2 agonist requirements, and chaotic peak expiratory flow readings.

So this poorly controlled asthma was not associated with any active eosinophilic airway inflammation. The cytospin shown is entirely normal. And this patient had never had a severe asthma attack, but clearly had symptom-predominant disease.

In contrast, the patient on the right has a

diary card that looks very respectable, few symptoms, normal peak expiratory flows, and little use of beta agonists, but their sputum shows intense and severe eosinophilic airway inflammation. And this patient had had two near fatal asthma attacks.

So it seemed to us that symptoms and eosinophilic airway inflammation are rather separate features of this disease. And it's possible and we subsequently showed that in 40 percent of patients with severe asthma, there is no eosinophilic airway inflammation. These patients have no potential to respond to a treatment that targets eosinophilic airway inflammation.

The other thought was it appeared to us that the presence of active eosinophilic airway inflammation was much more closely linked to the occurrence of asthma attacks than day-to-day symptoms and abnormal airway function, and this illustrates -- these cases illustrate that very nicely.

Now, what became a crucial question for us is what should be guiding anti-inflammatory treatment. Should it be symptoms and lung function, what we do traditionally, or should it in fact be objective measures of eosinophilic steroid-responsive airway inflammation? So should the patient on the left or the patient on the right get more treatment?

We set out to answer this question by comparing traditional symptom-guided management, which is labeled here as BTS for British Thoracic Society guidelines management, shown in blue, and a different management approach where the only goal of steroid treatment was to suppress eosinophilic airway inflammation, shown here in red.

You will see that we achieved very good control of eosinophilic airway inflammation over the 12 months of the study, and that's shown in the top left. So the induced sputum eosinophil count was well within the normal range in the group randomized to inflammation-guided management.

This improvement in inflammation control was

not associated with any improvement in lung function, shown at the bottom left, or symptoms, which I have not shown here. But what we did see was a very marked and statistically significant reduction in the frequency of severe asthma exacerbations. So this seemed to us to strongly support the view that eosinophilic airway inflammation and exacerbations are linked.

So our model for severe asthma was that there were at least two problems these patients had, which were relatively independent; firstly, an abnormality of airway function, which drives symptoms and impaired lung function tests; and, secondly, a tendency for eosinophilic airway inflammation to develop, which is particularly strongly linked to the risk of exacerbations.

This model predicts that if you reduce eosinophilic airway inflammation, the main impact will be a reduced risk of asthma exacerbations rather than an improvement in symptoms and lung function.

At about the time that were having this

insight, the early clinical trials of mepolizumab began being reported, and these were tremendously disappointing. Whilst the drug had a marked suppressive effect on eosinophilic airway inflammation -- if you look at the top left, you will see that the induced sputum eosinophil count was suppressed markedly and for a month after one injection of 10 milligrams per kilogram of mepolizumab, but this marked biological effect had no clinical effects. So there was no improvement in airway responsiveness, a good test of abnormality of airway function in asthma.

Then a subsequent larger clinical trial looking at morning peak expiratory flow as a readout, there was no evidence that 2 doses of mepolizumab improved lung function.

So I think the only people that weren't surprised by these findings were us, because our model predicted this. There seemed to be two fundamental issues with these studies.

Firstly, we didn't know that all the patients had eosinophilic airway inflammation

because it wasn't measured; and, secondly, the wrong outcome measure had been assessed. The main impact of reducing eosinophilic airway inflammation would have been the reduced risk of asthma attacks.

So we were delighted when GSK allowed us to look at mepolizumab in the population of patients who we knew, based on sputum analysis, had active eosinophilic airway inflammation, and this population also had a history of severe asthma exacerbations. So they had the clinical event that is linked to the pathology. And our trial was powered on a sufficient duration to show an effect on asthma exacerbations in this population.

Mepolizumab was given monthly for 12 months, and it achieved a marked and sustained reduction in blood, shown on the left, and sputum eosinophil counts. This was anticipated and had been shown before.

But what we did see, and which hadn't been shown before, was a very significant carving of the rates of severe asthma exacerbations. These are episodes requiring emergency unscheduled

prednisolone, and a particularly striking reduction in patients who had very frequent exacerbations, like the patient I told you about.

This improvement in exacerbations was not associated with any change in post-bronchodilator FEV1, shown on the left, or any significant change in asthma symptoms quantified as a Juniper Asthma Control Questionnaire score, shown on the right. And this score, incidentally, the lower the number the better, and a figure below 1.5 is generally regarded as controlled asthma.

We did see a small but statistically significant improvement in asthma-related quality of life assessed using the AQLQ questionnaire. On this questionnaire, higher numbers are good. So you can see, with mepolizumab shown in orange, a small but significant improvement over the 12 months of the study.

In a paper that was published in the same issue of the journal and was from McMaster and involved Freddy Hargreave, my old mentor, looked at a smaller population of patients, but, again, a

population that had severe eosinophilic asthma.

These were patients that required regular oral prednisolone, like the patient I told you about, to control their disease. And this was a 20-week study, which looked at the potential for mepolizumab to be oral steroid-sparing, meaning allowing patients to maintain control of their asthma despite lower doses of prednisolone. And the bottom line was that it did.

So patients randomized to mepolizumab were able to achieve an 84 percent reduction in prednisolone dose compared to 44 percent with placebo. And despite being on a lot less treatment, these patients experienced significantly fewer asthma exacerbations and had better symptoms and lung function.

So this is a new direction for patients with severe asthma and that presents challenges to the clinical community. We need to think about disease in different ways. Our assessment needs to include an assessment of current symptoms, shown here on the Y-axis, but also an assessment of the risk of

asthma attacks, and that can be quantified partly by assessing eosinophilic airway inflammation.

If we assess symptoms and risks, we can then individualize our approach to management. And I believe that specific inhibition of eosinophilic airway inflammation with mepolizumab will be an important treatment option for some patients based on the assessment of symptoms and risk.

It certainly made a big difference to the patient I told you about. She was fortunate to be randomized to the 575 phase 3 trial of 100 milligrams of subQ mepolizumab.

This is a study that investigated the oral corticosteroid-sparing effects of treatment. And on treatment and subsequently, she was able to reduce the daily dose of prednisolone from 20 milligrams to 5 milligrams a day. This allowed her to lose much of the weight she had gained on treatment, so she had a 56-pound weight loss, and there was a marked reduction in the other side effects. She had no asthma exacerbations, she noticed an improvement in her nasal and sinus

symptoms on treatment, and her post-bronchodilator FEV1 improved by a marked 400 mLs.

Now, I was in my old hospital in Leicester recently. And I'd bumped into this patient in the corridor, and I didn't recognize her because she didn't have all her kids with her and she had lost so much weight. But she stopped me and she said, "This treatment, I feel I've got my life back. I had completely lost control of my life when I was on prednisolone, but I feel like I've got it back." And that had a big impact on me. Thank you.

I would now like to pass on to Hector Ortega, who is going to tell you about the phase 2b and phase 3 studies of this agent.

Applicant Presentation - Hector Ortega

DR. ORTEGA: Thank you, Dr. Pavord.

Good morning. My name is Hector Ortega, and I'm the physician leading the mepolizumab clinical development program. I'm also an allergist with experience in the treatment of patients with asthma. I have been interested in severe asthma for a number of years, including my tenure at the

NIH, while working with the Severe Asthma Research Program, also known as SARP.

I will now review the efficacy results of our mepolizumab clinical development program in severe asthma and the eosinophilic inflammation.

I will use this slide to align my presentation. I will describe how the dose and subcutaneous route of administration was selected. I will then review the studies design to show the impact of treatment on reducing exacerbations and related outcomes.

I will then describe the process in data which identifies the patient likely to respond to treatment. Finally, I will review the data describing the oral corticosterioid-sparing effect of mepolizumab.

Let's first take a look at the dose selection information. Study 092 was a 12-week dose-ranging study that evaluated the pharmacokinetics and pharmacodynamics of mepolizumab doses administered subcutaneously and also by IV administration.

The pharmacodynamic endpoint or the suppression of blood eosinophils from baseline inform only dose to study in phase 3. Study 092 examined the pharmacodynamic effect of mepolizumab at subQ doses of 12.5, 125, and 250 milligrams, shown in dark blue; 75 milligrams was administered IV in this study, which is shown in light blue.

The 75 milligrams IV dose gives comparable exposure to the 100 milligram subQ dose based on bioavailability. This figure shows the reduction of eosinophils by dose as a ratio to baseline on the vertical axis. The horizontal axis displays the subQ dose of mepolizumab in milligrams. The results show a dose-dependent reduction of blood eosinophils, and the 12.5 milligram dose clearly show a limited effect.

We used this data to develop a model, shown now. The solid line shows the estimated eosinophil reduction in relation to dose, and the dotted lines show the 95 percent confidence interval.

Mepolizumab 100-milligram subQ, or equivalent mepolizumab 75 IV, produced 90 percent

of the maximum inhibition of blood eosinophils, also known as the ID90, which is shown by the green lines. Since the pharmacodynamic goal of mepolizumab is to reduce blood eosinophils, the 100-milligram dose was carried into the subsequent clinical development program.

In the next few slides, I will review the efficacy results from the two large exacerbation studies, 997 and 588. For context, exacerbations were defined as worsening of asthma, which required intervention with oral or systemic corticosteroids and may have required an emergency department visit or hospitalization.

Both studies compared mepolizumab with placebo added to the patients' standard of care therapy, which was defined as high-dose ICS plus at least one addition of controller.

Study 997 was a 52-week study comparing 3 doses of mepolizumab with placebo, all administered IV every 4 weeks. The second exacerbation study, 588, was a 32-week study evaluating comparable doses of mepolizumab

administered either IV or subQ.

The inclusion criteria for this study included the following: all patients were receiving high-dose ICS of at least 880 micrograms of fluticasone propionate or equivalent, plus another controller. In addition, all patients experienced two or more exacerbations in the past 12 months and had an FEV1 less than 80 percent predicted.

In study 997, patients had to have evidence of eosinophilic inflammation as shown by one of the following at screening or in the previous year: blood eosinophils of at least 300 cells, or sputum eosinophil count of at least 3 percent, or exhaled nitric oxide of at least 50 parts per billion, or a rapid loss of asthma control after less than 25 percent reduction in inhaled or oral corticosteroids.

For study 588, patients had to have a history of blood eosinophils of at least 300 cells or a blood eosinophil count of at least 150 cells at the screening.

Now, let's take a look at the

characteristics of patients enrolled in these studies. Both studies targeted patients with severe asthma and eosinophilic inflammation. Across the global program, the mean age was 50 years and the majority were female and white.

Individuals of African descent in the U.S. cohort represented about 25 percent of the patients. For reference, the CDC reports that about 15 percent of patients with asthma in the U.S. are African-American.

Approximately one-half of these patients were atopic and the geometric mean of eosinophil values were 250 cells in study 997 and 290 cells in study 588. Baseline asthma characteristics were similar between studies. Patients had a diagnosis of asthma for over 19 years.

To highlight the severity in this patient population, patients reported 3.6 exacerbations in the previous year. In addition, 44 percent and 33 percent of patients in studies 997 and 588 required either an emergency room visit or hospitalization in the prior year.

The percent predicted FEV1 and the FEV1/FEC ratio were low and characteristic of patients with severe asthma. And Asthma Control Questionnaire, or ACQ, score above 1.5 suggests poor asthma control. The mean scores in the exacerbation studies were 2.2 and 2.4, indicating lack of asthma control in these patients.

Let's now transition to the data demonstrating the impact of mepolizumab in these patients. I would like to start by showing you the side-by-side figures of the cumulative exacerbations over time in studies 997 and 588.

On the left is study 997 and on the right is study 588. The total number of exacerbations is displayed on the vertical axis and time is displayed by weeks on the horizontal axis.

The cumulative number of exacerbations for patients receiving mepolizumab and placebo are shown by dose and route of administration using the color codes and legend.

Patients receiving placebo plus optimized standard of care experienced 280 exacerbations over

52 weeks and 216 exacerbations over 32 weeks in studies 997 and 588, respectively.

The key observation across both studies is that treatment with all doses of mepolizumab consistently decreased the number of exacerbations by approximately 50 percent.

On the previous slide, I showed you the cumulative number of exacerbations over time. Now, I would like to show you the relative rate of exacerbations for mepolizumab compared with placebo for each phase 3 study.

On the left side of the figure, the dose and route of mepolizumab is depicted within the box. The exacerbation rate is compared with placebo, including the 95 percent confidence interval. If the confidence interval does not cross 1, then the result is considered statistically significant.

There was a consistently significant decrease for all doses of mepolizumab for every comparison versus placebo. For study 997, shown at the top, the rates of reduction ranged from 39 percent to 52 percent. In study 588, the rates

of reduction ranged from 47 percent to 53 percent, and mepolizumab administered either IV or subQ was comparable. Lastly, the integrated results in the bottom box combine all doses and routes of administration and shows a 47 percent reduction in exacerbations.

This slide describes the subset of more severe exacerbations that led to emergency department visits or hospitalization. As expected, with fewer events, the confidence intervals will be wider. Therefore, there is greater value in understanding and interpreting these events in a meta-analysis, shown in the integrated summary at the bottom of the slide.

In study 997, mepolizumab reduced exacerbations requiring ED visits or hospitalizations by 42 percent to 60 percent. In study 588, mepolizumab 75 IV and 100 subQ produced 32 percent and 61 percent reduction, respectively. Lastly, the integrated results demonstrated an overall 40 percent reduction in the rage of these exacerbations.

Now, let's examine exacerbations that required inpatient hospitalization. These are the results of the least frequent but most serious subset of exacerbations requiring only hospitalization. Study 997 demonstrated a reduction in the rate of exacerbations requiring hospitalizations of 35 to 63 percent. Each of these point estimates are clinically relevant for all doses.

In study 588, a 39 percent reduction in the rate of hospitalizations was shown for the 75 IV dose, and a statistically significant 69 percent reduction was shown for the 100-milligram subQ dose. The integrated results demonstrated a 51 percent reduction in exacerbations requiring hospitalization.

Now, I would like to briefly present the reduction in exacerbations based upon various subgroups. Subgroup analysis inform on whether the treatment effect is consistent across subgroups, and it is important to remember that these analyses are not necessarily expected to show statistical

significance.

For subgroups, integrated analyses are more informative than results from individual studies due to the increase in sample size. For reference, the 47 percent reduction in exacerbations in the overall population is displayed at the top in blue.

In this subgroup based on age, race, gender and region, there is a consistent response of approximately 50 percent reduction in exacerbations. The majority of these subgroups were well represented with over 100 patients. However, there were two subgroups that had limited representation, adolescents aged 12 to 17 and African-Americans.

There are no known reasons to believe that the responses to mepolizumab shall differ in the subgroups. The eosinophilic signature is present in these patients. Furthermore, the pharmacokinetic and pharmacodynamic characteristics in adolescents and African-Americans are similar to the overall population.

In adolescents, the severe asthma phenotype

with the eosinophilic inflammation is less prevalent than in adults. Therefore, it is not unexpected that there will be a small number of adolescents in this subgroup. As expected, the reduction in exacerbations is similar to that seen in the overall population.

Likewise, for African-Americans, the reduction in exacerbations is similar to the overall population. There were discordant responses in studies 997 and 588, but when the results are assessed as an integrated data set, the results provide reassurance of efficacy in this subgroup.

Due to the high unmet medical need in these subgroups, it is critical that effective medicines are available for adolescents and African-Americans with severe asthma.

In addition to the exacerbation endpoint, we also look at the effect of mepolizumab in other outcomes, including quality of life, asthma control, and lung function.

Next, I will review the effect of

mepolizumab on the impact of quality of life as measured by the St. George's Respiratory Questionnaire, or SGRQ.

The SGRQ is a well established self-administer instrument designed to measure quality of life in patients with obstructive airways diseases, including severe asthma and COPD. The questionnaire focuses on elements that are important to patients with severe asthma.

First, the questionnaire includes topics related with daily functional limitations; second, topics related with the impact on daily living; and, third, questions about attacks of shortness of breath and respiratory symptoms.

The SGRQ results from study 588 show significant improvements over placebo for patients receiving mepolizumab. On the vertical axis is the change from baseline in SGRQ score at week 32. A lower SGRQ score indicates improvement in health status, and any reduction of at least four units is considered clinically meaningful. Significant improvements in quality of life from baseline were

seen in all treatment groups.

When compared with placebo, both the 75 IV and the 100 subQ doses show remarkable and consistent improvement in SGRQ, as shown by the greater reductions of 6.4 and 7 units, respectively. These differences from placebo well exceeded the minimum clinically important difference of 4 units.

This was the first study in the program to utilize the SGRQ. I will show you additional results with the SGRQ when we review the data from study 575, the steroid-sparing study.

Next, I will review the Asthma Control Questionnaire results.

The Asthma Control Questionnaire, or ACQ, is a commonly used measure of asthma control focusing on daily symptomatic aspects of asthma rather than experiences related to changes by patients with severe asthma who frequently exacerbate.

An improvement in asthma control is indicated by a decrease in the score. The minimum clinically important difference, or MCID, is a

decrease in a score of 0.5.

In study 997, patients experienced modest improvements in asthma control. The 250 IV dose showed a statistically significant improvement, while the mean changes for all treatments did not exceed the MCID.

In study 588, both the 75 IV and the 100 subQ doses achieve a statistical significance and the treatment effects compared with placebo approach the MCID threshold. When all doses of mepolizumab are integrated from both studies, the decrease in score was 0.34.

Finally, we examined the effects of mepolizumab compared with placebo on lung function, as measured by the change from baseline in pre-bronchodilator FEV1. In study 997, we saw treatment differences of 61 to 81 mLs compared with placebo. In study 588, statistically significant differences from placebo of approximately 100 mLs at week 32 were observed with both the 75 IV and the 100 subQ doses. When all doses of mepolizumab are integrated, a statistically significant

difference of 84 mLs is achieved.

Now that I have shown you the results of the primary and secondary endpoints, I am going to transition the discussion to how we identify the biomarker employed in this program.

It is critical when developing medicines to identify which patients may benefit. On the next slide, I will review the data-driven approach that was used to identify and understand which patients derive benefit from mepolizumab.

A key goal was to assess whether a biomarker, other than sputum eosinophils, can identify patients likely to achieve a clinically meaningful reduction in exacerbations. This is important since induced sputum is more invasive, time-consuming, and only can be performed at specialized centers.

In study 997, we use four criteria to identify patients with eosinophilic inflammation, as shown on this slide. We conducted a modeling and extensive subgroup analysis to predict which patients derive benefit from treatment. The full

scope of this work is described in your briefing book.

This statistical investigation ultimately identified blood eosinophils as the single best predictor of treatment response. It is worth mentioning that other variables, including sputum eosinophils or exhaled nitric oxide, did not show this strong correlation.

The results demonstrated that mepolizumab treatment should be targeted to patients who had a history of frequent exacerbations despite the use of high-dose ICS plus at least one additional controller. In addition, this medicine should be targeted to patients with a blood eosinophil count of at least 300 cells in the previous year or at least 150 cells at baseline.

On the next slide, I will show you the basis of the selection of the 150 threshold and why we believe the inclusion of the historical threshold is appropriate.

This slide shows predicted exacerbation rates of studies 997 and 588 on the vertical axis

as a function of baseline eosinophil levels on the horizontal axis. This modeling analysis shows increased benefit with increased eosinophil baseline level.

At 150 cells per microliter in study 997, the reduction is estimated to be 30 percent, which is a clinically relevant reduction. In study 588, the reduction is estimated to be 39 percent. In other words, at least a 30 percent response is expected in patients at the lower end of the proposed baseline blood eosinophil threshold, whereas for the population as a whole, recall that a 50 percent reduction has been demonstrated.

Subgroup analysis of patients with a history of blood eosinophils of at least 300 in the previous year also derive benefit from mepolizumab. Since this subgroup represents only 13 percent of the total population, the studies have been combined.

The analysis shows that patients with a historical blood eosinophil value of at least 300 cells and a baseline value below 150 cells, there

was a clinically meaningful 33 percent reduction in exacerbations. This slide summarizes the expected reductions in exacerbations when the two blood eosinophil criteria are used in clinical practice.

Patients who did not meet either criterion in study 997, only a 10 percent reduction in exacerbations was observed, and thus mepolizumab is not intended for these patients.

In study 588, no data are presented, as all patients were required to meet either the baseline or historical eosinophil criteria. For patients who met the baseline threshold of at least 150 cells, mepolizumab reduced exacerbations by 54 percent to 53 percent, respectively, in studies 997 and 588.

For patients who met the historical threshold of at least 300 cells, mepolizumab reduced the exacerbation rate by 51 percent and 49 percent, respectively, in studies 997 and 588.

Let's now talk about the oral steroid-sparing study. Study 575 was a 24-week oral corticosteroid reduction trial. Patients with

severe asthma treated with regular prednisone are at risk of untoward effects associated with corticosteroid use in addition to the exposure received for treatment of exacerbations.

This is of great concern for patients and physicians due to the multiple side effects, such as diabetes, hypertension, infections, and weight gain, which are all associated with the chronic use of prednisone. The aim of physicians treating these patients is to avoid the use of prednisone and where required to utilize the lowest dose over the shortest period of time.

Study 575 randomized 135 patients to receive either add-on mepolizumab treatment or placebo over 24 weeks. The study treatments were added to the current therapy. At baseline, all patients were receiving daily prednisone in addition to the high-dose ICS plus another controller. All patients met the blood eosinophil threshold of at least 300 cells historically or the 150 at baseline.

The study included four phases. During the

optimization phase, baseline prednisone doses were adjusted weekly according to a titration schedule to achieve the lowest possible dose that was able to maintain asthma control. Asthma control was assessed using the ACQ.

During the induction phase, patients were randomized to receive either mepolizumab 100 or placebo and no titration of prednisone was allowed.

During the OCS reduction phase, the dose of prednisone was titrated by a fixed-dose algorithm every 4 weeks up to and including week 20.

Finally, during the maintenance phase, no further adjustment was made in the prednisone dose.

The primary objective of this study was to compare the effect of mepolizumab and placebo in allowing the reduction of maintenance prednisone in patients who are dependent on this treatment.

Here are the demographic and baseline characteristics. The mean age for each group was approximately 49 years, and there was a higher percentage of females in the mepolizumab group. The reported mean duration of asthma was about

20 years for both groups. A daily dose of prednisone above 5 milligrams can be associated with short- and long-term adverse effects.

The median dose OCS after optimization was 12.5 milligrams for placebo and 10 milligrams for mepolizumab. The health consequences of daily OCS use are even more important in this patient population since nearly 50 percent of all patients have been on daily oral corticosteroids for more than five years.

The geometric mean of eosinophil values were 230 cells in the placebo group and 250 cells in the mepolizumab group, which are similar to values that we presented from exacerbation studies.

The primary endpoint of the study was the percent reduction in daily prednisone use by defined dose-reduction category. The predefined categories included ranges from 100 percent reduction to no decrease in the prednisone dose from the dose at the end of the optimization phase.

The comparison between mepolizumab and placebo across all categories was statistically

significant, showing that patients on mepolizumab were able to achieve greater reductions in the steroid dose than those on placebo.

The odds for a patient receiving mepolizumab, they achieved greater reductions in prednisone dose by category 2.4 times higher than dose compared with placebo.

The secondary endpoints are useful in quantifying the benefit of the primary endpoint. Significantly, more patients receiving mepolizumab achieved a reduction of more than 50 percent reduction in their prednisone dose. In addition, significantly more patients were able to reduce their prednisone dose to 5 milligrams or less per day. The median OCS dose reduction was zero percent in the placebo group compared to 50 percent in the mepolizumab group.

The percent of patients who reach a complete reduction of their prednisone dose also favor mepolizumab, but the percent of patients in either treatment was low.

Patients treated with placebo were able to

reduce their prednisone dose form 12.5 milligrams to a median of 10 milligrams. In contrast, patients treated with mepolizumab were able to reduce their dose of prednisone from a starting dose of 10 milligrams to a median of 3.1 milligrams.

Additional endpoints support the positive benefits of mepolizumab in patients dependent on the use of systemic corticosteroids. Mepolizumab produced a statistically significant 32 percent reduction in the rate of exacerbations, and mepolizumab produced a 114 mL improvement in FEV1.

In addition, a significant improvement in the ACQ was demonstrated, which surpassed the MCID. Similarly, improvements in the SGRQ quality of life instrument also surpassed the MCID.

It is important to remember that these treatment effects were obtained on much lower doses of prednisone compared with the standard of care.

Overall, the effectiveness of mepolizumab is compelling. To help summarize the efficacy results, all doses and routes of administration

from endpoints common to both exacerbation studies 997 and 588 have been integrated.

When mepolizumab is added to optimize standard of care, this new treatment reduced exacerbations requiring systemic corticosteroids, as well as a subset of exacerbations requiring ED visits or hospitalizations by approximately 50 percent.

What does that mean for the patient? Well, during the phase 3 program, patients receiving placebo experienced 504 exacerbations. Had this group benefitted from the 47 percent reduction in exacerbations, they could have been spared approximately 240 exacerbations. This is clinically compelling as exacerbations are frequent and unpredictable disruptions in the lives of patients with severe asthma.

If we extrapolate this data, a patient on mepolizumab will experience five exacerbations every 5 years, while patients on standard of care will continue to experience 10 exacerbations every 5 years. Likewise, patients receiving mepolizumab

will experience one hospitalization every 11 years compared to one hospitalization every 6 years for patients receiving standard of care.

Improvements in other markers important to patients with asthma were also observed, including lung function and asthma control, as assessed by the ACQ.

As we discussed, severe asthma can greatly disrupt the day-to-day life of patients and their families. For example, patients are physically limited by the disease, and their lives are impacted by avoiding work or social situations that could trigger an asthma attack.

Results of the SGRQ show that mepolizumab treatment produced substantial and clinically relevant improvements in the quality of life of these patients. Consistent with treatment guidelines, the key goal of managing patients with asthma is to avoid the use of prednisone and, when required, to utilize the lowest dose over the shortest period of time.

Study 575 demonstrated statistical and

clinical relevant reductions in the requirements for daily prednisone use in patients who have been dependent on daily prednisone. Taken together, the efficacy results demonstrate that mepolizumab provides significant benefits for patients with severe asthma and eosinophilic inflammation who currently have very limited treatment options.

I would like now to turn the podium over to Dr. Leadbetter, who will review the safety data.

Applicant Presentation - Robert Leadbetter

DR. LEADBETTER: Good morning. I'm Bob Leadbetter. I'm a senior physician and lead physician in the safety group at GSK, and I'm pleased to be here this morning to talk to you about the safety profile and the benefit/risk profile of mepolizumab.

This slide is familiar to you from prior presentations. I will begin by discussing the integrated safety information obtained from the three key pivotal double-blind, placebo-controlled trials, followed by the data from the open-label extension studies.

This presentation will focus on the adverse events observed with a 100 milligram subQ and the comparable dose of 75 milligrams IV. As you have seen, mepolizumab 250 milligrams and 750 milligrams IV were also evaluated during then program. Therefore, I will show you data from all doses of mepolizumab combined.

Fifteen hundred and ninety-six asthma patients have been exposed to mepolizumab across all asthma studies. In the severe asthma program, 1,018 patients received 100 milligrams subQ and 344 patients received 75 milligrams IV. In total, we had more than 1,000 patient-years of exposure at relevant doses in the severe asthma trials. Furthermore, 526 patients have received mepolizumab for a duration of 12 months or greater.

The overall patient exposure from the severe asthma program, including the number of patients treated for 12 months or greater, is consistent with the ICH guidelines to characterize the safety profile of a new drug.

This slide presents the outline of my talk.

GSK identified adverse events of special interest that might be associated with mepolizumab treatment due to its pharmacologic properties, mechanism of action, or areas of clinical concern for this population.

For example, it is plausible that a monoclonal antibody could be associated with systemic reactions such as hypersensitivity, injection site reactions, or development of anti-mepolizumab antibodies. Furthermore, it is unknown if decreasing the eosinophils could impact immune system function. Thus, we prospectively monitored infections and malignancies.

Cardiovascular safety was also included as an adverse event of special interest due to observations in the early dose ranging 997 study and since mepolizumab is a first-in-class medication targeted to a patient population that tends to be older and may have increased cardiovascular risk factors.

After discussing the adverse events of special interest, I will review the overall adverse

event profile of mepolizumab, including serious adverse events and fatal events. I will also present data regarding the safety profile of subgroups of patients, such as age, race, and gender.

In addition, I will provide an overview of the safety information from the ongoing open-label extension studies, which provide additional long-term safety information to supplement the data from the placebo-controlled program.

We will demonstrate that mepolizumab has a favorable safety profile with no evidence of off-target adverse effects. I will conclude my talk by summarizing the positive benefit/risk profile of mepolizumab.

During the development of mepolizumab, investigators were requested to prospectively assess systemic reactions to characterize allergic and non-allergic reactions. Anaphylaxis was assessed by utilizing standard diagnostic criteria as outlined in the 2006 NIH-sponsored symposium on anaphylaxis.

As you can see, the rate of events of systemic hypersensitivity as well as non-allergic reactions to mepolizumab was similar to placebo. With the exception of one report of a serious delayed hypersensitivity reaction from open-label study 661, all hypersensitivity events reported across the program were non-serious. Notably, there were no reports of anaphylaxis considered possibly related to treatment with mepolizumab.

Local injection site reactions were reported in 8 percent of patients receiving mepolizumab subcutaneous injection compared to 3 percent with placebo. This adverse reaction is not surprising following a subcutaneous administration. Nonetheless, all injection site reactions were reported as non-serious and were of mild or moderate intensity.

I would now like to review the immunogenicity profile. Because mepolizumab is a humanized monoclonal antibody with extensive sequence homology, the potential for immunogenic responses in humans is low. Six percent of

patients treated with 100 milligrams subQ and 3 percent of patients treated with 75 milligrams IV developed anti-mepolizumab antibodies after receiving at least one dose.

Importantly, patients developing mepolizumab -- who developed anti-mepolizumab antibodies did not show evidence of loss of efficacy or change in pharmacokinetic or pharmacodynamic characteristics. In these patients, there were no events of drug hypersensitivity, anaphylactic reactions, or delayed hypersensitivity.

Development of neutralizing antibodies has the potential to inhibit or reduce the effectiveness of mepolizumab or to be associated with adverse effects. One patient developed neutralizing antibodies. This patient was receiving 100 milligrams subQ and developed eczema and an injection site reaction. The patient withdrew from the study and the events resolved.

Eosinophils are a component of innate immunity, but are not directly involved in adaptive

immune responses. As mepolizumab only binds to IL5, it should not impact T-cell or B-cell function nor the generation of antibody response to antigens. Furthermore, mepolizumab treatment is not associated with complete ablation of circulating eosinophils. Hence, any effect on their role in innate immune response should be minimal.

There was no preclinical evidence suggestive of an increased risk of infections associated with mepolizumab. In the randomized control trials, the rate of infections and infestations was similar between mepolizumab and placebo. The most frequent infection adverse events were nasopharyngitis and upper respiratory tract infections, as is often seen in asthma studies.

Pneumonia-related events were the most frequent infectious serious adverse event and occurred in less than 1 percent of patients across all treatment groups. Because these patients are receiving a biologic in addition to high-dose corticosteroids, we also examined the incidence of

opportunistic infections. Events were infrequent and similar to placebo.

The development of neoplasms, both benign and malignant, were infrequent and consistent across treatment groups. Malignancies are rare reported and the types of malignancies reported were those that are common in the general population, including common skin cancers and prostate cancer. None of the types of malignancies were reported in more than one subject.

In preclinical toxicology studies, mepolizumab was not associated with evidence of cardiac or vascular pathology. During the clinical development of mepolizumab, there was no evidence of clinically relevant changes in blood pressure or pulse. EKGs were evaluated throughout the course of the program, and there was no evidence of clinically relevant EKG changes or prolongation of the QT interval.

In this summary table of integrated, randomized, controlled studies, cardiac and vascular adverse events are categorized by system

organ class, or SOC, utilizing the standard regulatory dictionary. As you can see, there was no evidence of an imbalance of adverse events in the cardiac and vascular SOCs.

The number of serious events in these categories was low. In order to summarize all relevant serious adverse events of a cardiac, vascular, or thromboembolic nature, we included additional relevant terms from other SOCs; for example, stroke from the nervous system disorder SOC. Combining all relevant serious cardiac, vascular, and thromboembolic events, the rate of these events was similar to placebo.

Next, I will transition to review the adverse events and serious adverse events from the randomized controlled trials. I will also review the deaths from the severe asthma program and describe the additional long-term safety data from the open-label extension studies.

Adverse events that have been reported in 5 percent or more of patients treated with 100-milligram subQ or 75 milligrams IV are shown

here. Overall, adverse event were reported for approximately 80 percent of all patients. The most common reported non-serious adverse events were headache and nasopharyngitis.

Other than injection site reactions, as mentioned previously and shown on the bottom row, common adverse events reported were largely similar between placebo and mepolizumab. Though not shown on this table, there was no evidence of treatment-related effects on clinical laboratory tests, including enzymes.

The incidence of serious adverse event was 6 percent for mepolizumab 100 milligrams subQ and 10 percent with 75 milligrams IV compared to 15 percent with placebo. Not surprisingly, the most frequent serious adverse event was asthma exacerbation, with a higher rate associated with placebo treatment.

When asthma events are removed, the incidence of serious adverse events was comparable between placebo and mepolizumab. There was no apparent imbalance in the incidence of other

serious adverse events; the numbers were small. While not shown on this slide, the incidence of withdrawals due to adverse events and drug-related adverse events were low and comparable to placebo.

As Dr. Pavord pointed out, patients enrolled in these studies were at increased risk for fatal events due to their severe asthma; 19 to 25 percent of patients required hospitalization in the 12 months prior to study enrollment. Furthermore, in the prior year, 8 to 14 percent had had a life-threatening event and 3 to 8 percent required intubation. Additionally, these patients have other risk factors, including complications associated with oral corticosteroid use and obesity.

There were 8 deaths, 5 in the placebo-controlled severe asthma trials and 3 in the open-label extension studies. No deaths were attributed to study treatment. Two patients treated with placebo died and 3 deaths occurred in patients receiving mepolizumab in the randomized control trials.

One patient on placebo died in a traffic accident and a second was hospitalized following an asthma exacerbation, developed a lung fungal infection, acute GI hemorrhage, and died due to aspiration.

One patient receiving 250 milligrams IV mepolizumab developed acute asthma attack resulting in severe cerebral hypoxia. Another receiving 250 milligrams IV developed pancreatitis and septic shock. And a patient on 750 milligrams IV committed suicide.

Three deaths in the open-label extension studies occurred in patients receiving 100 milligrams subQ, one due to respiratory arrest subsequent to an asthma exacerbation, one from complications of morbid obesity, and one from acute cardiac failure.

You will recall that Dr. Ortega presented efficacy by subgroups. We also examined the corresponding safety profile by types and frequencies of adverse events, serious adverse events, and adverse events of special interest. I

would now like to show you the serious adverse event data by subgroups of age, race, and gender. As with all subgroup analyses, comparisons between treatment groups should be made with caution.

Nineteen adolescents received mepolizumab and 9 received placebo in the randomized trial. Two serious adverse events were reported in adolescent patients receiving placebo. Both were asthma exacerbations. Two serious adverse events were also reported in patients receiving mepolizumab, one an asthma exacerbation and one event of eczema, which resolved while mepolizumab was continued.

The frequency and types of non-serious adverse event were also similar to those seen in adults. Furthermore, among those aged 65 or older, the adverse event profile was similar to the overall population.

Thirty African-American patients received mepolizumab and 9 received placebo. As seen in the overall population, more frequent asthma exacerbations were reported with placebo than with

mepolizumab. The remaining serious adverse events were similar in nature to those seen in the overall population. Finally, an examination of the adverse event profile by gender did not indicate differences between men and women.

Thus, a careful review across subgroups of the frequency and types of adverse events, including serious adverse events and adverse events of special interest, found no clinically meaningful differences between mepolizumab and placebo.

In addition to the data from the randomized control studies, which were up to one year in duration, we have further long-term safety data from 998 patients enrolled in ongoing open-label extension studies 666 and 661.

The total exposure to mepolizumab across the randomized phase 2 and 3 program and the open-label extension study program has now reached approximately 1900 patient-years. Patients have been treated with mepolizumab for up to 3 years, with a median treatment of 1 and a half years.

During the open-label extension studies, all

patients received mepolizumab 100 milligrams subQ. Over the open-label extension studies, the profile of adverse events and serious adverse events remain comparable with the profile seen in the phase 2 and 3 programs.

In addition, adverse events of special interest related to systemic reactions, injection site reactions, infections, malignancies and cardiac disorders, all remain comparable with the profile established during the phase 2 and 3 program. Importantly, there continue to be no reports of anaphylaxis.

Thus, the data from the long-term open-label extension studies show that multiyear treatment with mepolizumab did not alter the interpretation of the safety profile.

I will finish my presentation by summarizing the benefit/risk balance in patients with severe asthma with the eosinophilic inflammation. Dr. Ortega has shown that mepolizumab is consistently efficacious in patients with severe asthma with the eosinophilic inflammation.

Efficacy has been demonstrated and patients continued to have severe exacerbations despite optimized standard of care therapy. Treatment is associated with a marked decrease in asthma exacerbations, hospitalizations, and emergency department visits with resultant improvement in quality of life.

Response to mepolizumab was persistent with treatment, and we have shown the concomitant use of oral corticosteroids, which are associated with numerous and often serious adverse effects, can be diminished substantially with mepolizumab treatment, even while improving lung function and decreasing exacerbations.

We've also demonstrated that mepolizumab has a favorable safety profile. There is no observed increase in the adverse events of special interest, including systemic reactions, infections, malignancies, and cardiac disorders. Local injection site reactions were higher than placebo, but still relatively low at 8 percent.

Serious adverse events are reported at a

lower frequency with mepolizumab than with placebo, largely driven by the higher rate of asthma exacerbations and hospitalizations in the placebo arm, as we described in the efficacy population.

So in summary, we have compelling evidence that mepolizumab reduces the frequency of asthma exacerbations and can be targeted to appropriate patients utilizing a readily available laboratory test. By employing blood eosinophils as a guide for treatment, mepolizumab can be utilized in those most likely to respond, hence, minimizing risk.

I would now like to invite Mr. Yancey back to the podium for closing remarks.

Applicant Presentation - Steven Yancey

MR. YANCEY: Thank you, Dr. Leadbetter.

So this morning, we presented a clear scientific and clear clinical rational, as well as the positive benefit-to-risk ratio supporting the use of mepolizumab in patients with severe asthma and eosinophilic inflammation.

By utilizing blood eosinophils as a biomarker, it is possible to predict the patient

likely to respond to treatment. Using this biomarker, mepolizumab consistently demonstrated approximately a 50 percent reduction in exacerbations in the overall population, as well as in important subgroups, such as African-Americans and adolescents.

In addition, exacerbations requiring emergency department visits and even the most severe exacerbations requiring hospitalization were consistently reduced by approximately one-half.

Treatment with mepolizumab consistently produced improvements in quality of life and lung function. And furthermore, the medicine was shown to significantly reduce the requirement for daily oral prednisone, while maintaining or improving asthma control.

The clinical program was designed to robustly evaluate adverse events of special interest. The profile of adverse events of special interest was comparable with patients receiving placebo added to intensive standard of care therapy.

The overall adverse event profile of mepolizumab was consistent across the asthma program and generally similar, again, to patients receiving placebo added to optimized standard of care.

I'd like to leave you with a reminder about the patient waiting for treatments such as Nucala. Patients with severe asthma and eosinophilic inflammation represent a unique challenge to physicians who are unable to gain control of the disease in patients who are using optimized standard of care.

Taken together, the clinical program provides compelling evidence that Nucala is a new and effective therapeutic class that can vastly improve the lives of patients with severe asthma.

Thank you, and we would be happy to take any questions.

Clarifying Questions to Presenters

DR. SWENSON: Thank you for all of those presentations. We will now move to a session in which we will ask the sponsor any clarifying

questions. But before we proceed, I'd like to have Dr. Davi introduce herself. She just arrived at this point a bit late, with good excuse.

DR. DAVI: Sorry about that. Sorry about the late arrival. I actually thought we were at the Holiday Inn today. I'm Dr. Davi. I'm deputy director in the Office of Biostatistics at CDER, working on this application.

DR. SWENSON: Now, as we move to the clarifying questions, what I would like to ask is that all of you that have questions in some way catch Dr. Toliver's eye here. We'll try to take questions in order.

If you have a question, please state your name for the record before asking, and if you have a particular person in GSK that you would like to pose your question to, do so. If it is an open question, then, of course, we'll let them decide who might answer.

So we are now open for questions. Dr. Morrato?

DR. MORRATO: Thank you. This is

Dr. Morrato. My question relates to the question that FDA is asking us to consider, which is practical applications of targeting the patient population in a real-world setting.

I noted in the briefing document that in GSK's interactions with the agency, the agency had said that the clinical program should define a patient population that can be clearly described in the product label and readily identified in the real world. So my questions relate to better understanding your data with regard to that.

So my first question is you mentioned that the biomarker testing is readily available. Do you have data on the proportion of patients in the U.S. in community-based practice who have eosinophil counts in their charts in order to assess history and to assess how many will require baseline screening? That's my first question.

MR. YANCEY: So let me take that first question, then we can move to the second question.

I can answer that question with the data that were available within the clinical trial

program. So we have not looked outside into the larger community. But, again, these are patients that would represent the typical patient that would be treated by a physician who specializes in the management of severe asthma.

In our studies, exacerbation studies, 69 percent of patients had an historical record or common CBC count to allow the physician to make a judgment around that eosinophilia.

DR. MORRATO: Now, I recognize that this is a global program. So in the U.S., what was that percentage?

MR. YANCEY: I don't have that readily available to me. I'll look to my colleagues. No. We don't have that. We can look for that perhaps during the break.

DR. MORRATO: Yes. That would be helpful. In a typical clinical setting, these are academic centers that participated in your study or were these community-based asthma centers?

MR. YANCEY: It's very much a mixture. So it's a global program, as you pointed out. About

12 percent of patients were enrolled from the U.S. sites. These are sites that are primarily dealing with outpatient services. So they include primarily pulmonologists and allergists.

How the health care is delivered around various countries varies. So for example, in Europe, you may be in more specialized centers, whereas in the U.S. you may be in standard primary out there.

DR. MORRATO: I think it would be helpful to know what's the setting in the U.S. since our label is reflective of clinical care here.

MR. YANCEY: And the setting in the U.S. is not primarily academic centers.

DR. MORRATO: Great. My second question relates to figure 19, which was in the briefing document, which I think is slide A-51 in what you presented. I found this modeling very interesting, and I bring sort of an epi-diagnostic orientation to the analysis.

So I'd like to know what was the N that met the cut point you identified, and what would be the

positive predictive value of using that criteria to predict an adequate response, which I think you characterize as 30 percent exacerbation reduction?

MR. YANCEY: Just so I'm clear on that question, you said what would be the N, just the number of the patients.

DR. MORRATO: Yes.

MR. YANCEY: Yes. Okay. That's fine.

DR. MORRATO: That met the cut point.

MR. YANCEY: Sure.

DR. MORRATO: I'm trying to get at screening efficiency.

MR. YANCEY: I understand.

DR. MORRATO: And, therefore, from a practice standpoint.

MR. YANCEY: I understand that question. So if we look primarily at the data from the 997 study, recall patients did not have to have a requirement for inclusion of either 100 or 300, so that's a more selective population.

Let's look back at the 997 study, which in this slide would be indicated by the dash line and

the solid line in blue. These are patients that could enter based on criteria relative that would predict eosinophilic inflammation. And in that proportion of patients, about 25 percent of patients were below the 150 cell count, and therefore, 75 percent would have been higher.

DR. MORRATO: Okay. I was also looking at the *New England Journal of Medicine* articles and the consort diagrams.

MR. YANCEY: Yes.

DR. MORRATO: So if you're looking at those coming in screened versus those that got randomized, is it fair to say the rate that was lost was about 26-28 percent, which would be comparable to your 25? Am I right in triangulating that way? I know these other causes why they may not have gone forward.

MR. YANCEY: I understand. So now you're talking about the patients who did not make it into the model, for example. I'm actually going to have to trust your number on that because I'm not recalling the exact consort numbers that were

available from the 997 data from patients who did not qualify.

DR. MORRATO: And just one last clarifying, and then I'll stop.

MR. YANCEY: Yes.

DR. MORRATO: So recognizing that life in the real world may not reflect the wonderful care and attention to screening that's done in trials, what is GSK planning on doing when they commercialize and launch the product to ensure appropriate screening of patients is occurring, to make sure you have the right target? And what's the downside risk of providers wrongly treating? Either, A, they are not using the blood serum, they are just basing it on clinical markers.

So I'm just trying to understand the risk management plans in commercialization activities. And that will be my last question.

MR. YANCEY: So I'd really like to take the first part around how GSK may be able to manage the appropriate use of the medicine, and I think probably our best ally is the communication through

product labeling. And we will work very closely with the agency to ensure that the product label clearly identifies those patients who are likely to respond based on the data from these studies. Of course, that then becomes translated into how we interact with health care professionals in the community, and we are completely guided by that product monograph.

Your other question was around what would be the potential for the downside risk. I think if we consider the presentation from Dr. Leadbetter, I think we can probably agree that there would be limited downside risk. There would be no upside efficacy value, so the overall risk/benefit profile would be unusual in that circumstance.

So I think it really comes back to the first element that you described, and that would be the assurance of working closely with the agency to have a very well and very directed product label that will inform health care professionals so we would not have off-target use of the medication.

DR. SWENSON: Dr. Connett?

DR. CONNETT: Thanks very much. I'm John Connett, biostat. Slide A-43 shows severe exacerbations requiring hospitalization at 3 doses, 75 milligram, 250 milligram, and 750 milligrams IV. And the best of those and the one that is actually statistically significant is the 750 milligram.

So then when you talk about safety, although I think it was said that you were going to show us the safety information for all the doses that were tested, I didn't see much with regard to the 750 milligram.

I mean, a 65 percent reduction -- 63 percent reduction in hospitalizations versus 35 or 39 sounds like a useful difference.

So I'm wondering why you settled on this 100-milligram subcutaneous dose instead of going to the higher dose and whether there were safety issues associated with these higher doses that you really hadn't presented.

MR. YANCEY: So that's a multilayered question. I'm going to speak to the safety element in a very general term, and if you would like some

follow-up, I would invite Dr. Leadbetter back to the podium.

What we provided in our safety overview was a very careful look at the 75 and 100 milligram, both IV and subcutaneous, as the proposed commercialized dose, and then in the far right column were all doses. So that would have included studies that had both the lower doses of 75, 100 and 250 and 750.

Not showing the 750 data specifically, there was not any other suggestions of a dose-related adverse event profile related to the higher dose. So again, I'm going to answer that one firstly, and if you want to go into further detail, I would invite Dr. Leadbetter back to the podium.

You then were asking a question around subgroup analyses and how was a decision taken around trying to decide the most appropriate dose to move forward. Always talking to a statistician, I'm very careful. Sometimes I want to bring up my statistician, but I'd like to stake a stab at this firstly.

I personally am very careful at looking at a single subgroup or single subanalysis of an outcome. We looked very carefully at the dose-ranging study 997. You have selectively chosen an endpoint where the reduction in hospitalization was higher.

We look thoroughly at other endpoints or outcomes that could suggest whether or not there is a dose proportional relationship with regard to efficacy, the number of complete exacerbations, the number of ED visits, the length of hospitalization, other quality of life measures, the PROs.

We look across the breadth of those data, and there was not a suggestion that more severe exacerbations would be reduced by the highest dose. And I think that was really borne out when we look at the 5588 study. You may recall that the 5588 100-milligram dose alone produced a 69 percent reduction in hospitalizations.

DR. SWENSON: Mr. Yancey, could I just interrupt for a second? Could you have these slides brought up for us as you discuss them?

MR. YANCEY: I'm happy to do that. Slide up, please.

So I'll just bring you back to that last point I was making, and that was around the study 5588, which is shown in the middle portion of this particular figure. You can see that we also saw a 69 percent reduction in the hospitalizations with that dose.

So if you look back at 750 and look at this dose, I think this is really more an element of the standard variation, particularly when we look at smaller outcomes and not the primary outcome for which a study was designed.

DR. SWENSON: Dr. Dykewicz?

DR. DYKEWICZ: Can I see slide A-53, please? One of the questions that has been raised is the adequacy of data in adolescents and African-Americans that's being presented to us. Part of that question is the applicability of the use of these blood eosinophil cutoffs in adolescents and African-Americans.

Has there been a subset analysis of those

subgroups relative to the applicability of these eosinophil criteria and the impact on exacerbation rate?

MR. YANCEY: I understand your question. It's whether or not these same thresholds are applicable to specific subgroups. I think it's really important that we consider subgroups and we consider how subgroups inform.

So in this overall clinical program, it was designed around a global program, and it's really quite robust based on ICH guidelines. When I think about subgroups, I really think of three important elements, and those would be similarities of disease, similarities of the mode of action in PK/PD results, and then whether there are similarities with regard to outcomes such as response to efficacy and safety outcomes.

So when we look -- and you've asked specifically about African-Americans and adolescents. We look across those data, and it's primarily from very large pools of studies that look longitudinally at cohorts of patients with

severe asthma, we do see similarity of disease in adolescents as well as African-Americans compared to adolescents and non-African-Americans.

So they have that eosinophilic signature. The mode of action is the same, and the response in terms of PK/PD is the same or similar. And in addition, finally, the elements of efficacy were shown to be very similar.

I'm going to look toward Oliver Keene to ask if we specifically have subgroup analysis based on the subgroups. I did not think we did, which is why I was checking. We do not have those data to share with you with regard to analysis of this particular threshold based on African-Americans or adolescents, and that's primarily because when you get into such small groups, recalling that there are 39 African-Americans and 28 adolescents, those subgroup analyses become really quite unreliable.

DR. DYKEWICZ: Part of the concern, though, as Dr. Ortega has indicated, there are some differences between adolescents and adult patients in terms of the inflammatory cell profile. True.

And these studies being presented to us were designed to select patients who had an eosinophilic profile.

But we are understanding that there is greater complexity to the inflammatory cascade. There are some patients who, besides having the predominant eosinophil sputum signature, have neutrophils, some that have neutrophils plus eosinophils, and there is then the question about if you're looking at the adolescents, the small numbers that they are, are you looking at some different mix of eosinophils and neutrophils? And that is why I was looking for, particularly in adolescents, some subset analysis.

MR. YANCEY: I think since you have directed that question to Dr. Ortega, I will invite him to the podium to respond.

DR. ORTEGA: Just to address the question about whether the basic baseline characteristics in terms of eosinophils are relatively similar to the adult population or the overall population, we look at specifically the subset of patients at baseline

in terms of blood eosinophil levels, both African-Americans and adolescent patients.

So in general, they are similar, and, therefore, it's not surprising because these patients qualified on the basis of that criteria to the trial.

Now, we do not have data on the ratio of eosinophils and neutrophils, which might be another area. In our phase 3 program, we focus on blood eosinophils as the marker. Early studies, we have done on sputum characterization, but it was not applicable for these subgroups that you're asking for.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: Thank you. This is Paula Carvalho. I have a question on slide A-73. And the specific question is there are quite a few genetic polymorphisms between ethnic groups' interleukins. There is actually relatively little information on interleukin 5 specifically.

But what I'm wondering about is regardless of the low numbers of African-Americans, we have

straight across the board higher serious adverse events listed. And I'm wondering, were these asthma deaths or asthma events, or what variety were they?

MR. YANCEY: So, Dr. Leadbetter, please address that question.

DR. LEADBETTER: Thank you for your question. If we could have slide up. Thank you.

Of course, we looked carefully at this question around the adverse event profile in, of course, adolescents and African-Americans as part of preparing for this discussion. And you are correct. The frequency of serious adverse events is more frequent in African-Americans versus whites, but, again, very limited numbers.

The adverse event profile, particularly the serious adverse events, were largely driven, again, by asthma exacerbations and, again, more African-Americans had asthma exacerbations on placebo than mepolizumab. So that certainly is one sort of aspect of us trying to understand the safety profile.

There were a subset of individuals of African-American descent who continued on to open-label extension studies. Their safety profile appeared to be very similar in that extended period as in the randomized control trials.

Going back to serious adverse events, the other serious adverse events other than asthma exacerbations in African-Americans were single events. So, for example, there was an individual who had colitis and an intestinal perforation, a URI and those sort of events, but they were all singular. So there didn't seem to be a pattern, from what we could see.

One last thing I'll point out is we mentioned earlier the 006 study, which was the early study that was performed, and we did have 26 African-Americans in that population receive mepolizumab, 18 placebo, and we had one serious adverse event of appendicitis and, again, the AE rates were comparable.

So our overall summary and assessment of this looks to be that the African-American subjects

had a similar safety profile as the larger population.

The last thing I'll point is that certainly if we go forward with marketing on this product, we will be very careful in our pharmacovigilance to look specifically at subgroups such as African-Americans and adolescents and to look for any trends or evidence that there might be an imbalance during the marketing period.

DR. SWENSON: Dr. Follmann?

DR. FOLLMANN: Yes. Thank you. This is Dean Follmann from NIH. I had a couple of question related to labeling and the intended population.

The first one build on comments that Dr. Morrato had concerning A-51, slide A-51, which I also thought was a very thoughtful, interesting kind of analysis. And I had two questions related to this slide.

The first one, just so I better understand it, with 997, you were looking for ways to predict benefit to try and hone in on inclusion criteria or labeling criteria, ultimately. So I guess you did

an exercise where you considered baseline eosinophils and other factors, and ultimately decided eosinophils is what you wanted to look at.

Then you estimated the curves, I guess, in slide A-51, for the study 997, and then, in addition, used the other study, I guess 558, to give additional evidence of that.

So do I have that correct?

MR. YANCEY: You do have that sequence correct.

DR. FOLLMANN: All right. The comment I have then, it seems a little incomplete -- and this is also getting to what Dr. Morrato was talking about, because we see the estimated effects as a function of baseline eosinophils, but we don't have estimates of the uncertainty about the benefit.

So do you have a slide related to 51 that would show confidence intervals, the predicted benefit plus or minus within the 95 percent confidence interval, as a function of baseline eosinophil count?

MR. YANCEY: I think I would like to invite

our statistical lead, Oliver Keene, to the podium to address that.

MR. KEENE: I'm Oliver Keene from GlaxoSmithKline, clinical statistics. So you're asking about the eosinophil model. Can I have slide up, please?

So your specific question was around the confidence intervals for the estimated improvements.

DR. FOLLMANN: For the estimated benefit, yes. I prefer that to the confidence intervals on the rates you have there. I'm more interested in the difference between placebo and the treatment.

MR. KEENE: First of all, the confidence intervals for the rates -- if you take the 30 percent, with the confidence intervals there, they go from 0.5 -- well, 0.7 is the right ratio, so that's a 30 percent reduction.

So the lower confidence interval there is 0.53, which is a 47 percent reduction. The upper confidence interval is 0.93, a 7 percent reduction. So that's the confidence interval around the

30 percent. So it goes from 7 percent to 47 percent.

In terms of an absolute reduction in terms of the 997 data, you can read that from the slide. That would be about a half of an exacerbation per year at that particular cut.

DR. FOLLMANN: Do you have a confidence interval for the 39 percent, as well?

MR. KEENE: Yes. For the 39 percent, the confidence interval for that ranges from an 18 percent reduction to a 55 percent reduction.

DR. FOLLMANN: Okay. Thank you. My second question has to do with slide A-44. And once again, one of the things we're charged with is looking at adolescents and then African-Americans. And this slide shows the estimated benefit and confidence intervals for those two important subgroups.

So I had one question -- well, two questions. One is whether you stratified randomization by these subgroups. Sometimes with small subgroups, you can get imbalances in terms of

severity of underlying disease in the two different groups, so I was wondering if you stratified randomization by either those.

Then relatedly, did you do an adjusted analysis where you used baseline covariates to try and sort of correct for any imbalance and, based on that, come up with an estimated ratio and a confidence interval for an adjusted analysis?

MR. YANCEY: Oliver, I'm going to invite you back to the podium. I can answer your question quickly, and then we can move to the second portion of that question. We did not stratify based on these subgroups.

DR. SWENSON: Again, I'd ask if we could have the particular slides up as we are discussing them.

MR. KEENE: Slide up. So you're asking about these analyses and whether baseline covariates influenced the effects.

DR. FOLLMANN: Yes, basically.

MR. KEENE: Obviously, some of the covariates you can't fit as easily, by region, for

example, the African-Americans predominantly in the U.S. But when we looked at the other important covariates that predict a fact, the actual estimates are very stable. So if you do a covariates analysis that includes eosinophils and history of exacerbations, and whether the patient is on maintenance oral corticosteroids, you get very similar estimates for the pediatric population for the African-American population.

DR. SWENSON: Thank you. Dr. Georas?

DR. GEORAS: I have a comment and then two questions. One comment would be, just for point of clarification, I think the statement was made that the IL5 receptor or IL5's biologic activities are limited to eosinophils. But I believe that under some circumstances, B lymphocytes are also responsive to this cytokine.

But pertaining to the question at hand today, I'm concerned about moving eosinophilia into the real world as a biomarker. So my questions are, I would think, to Dr. Ortega and then Dr. Pavord, relate to the reproducibility of this

eosinophilia in the general population.

We know that eosinophils are markedly affected by corticosteroids, for example. So I would appreciate any information regarding stability of eosinophilia.

I mentioned Dr. Pavord because it's my understanding that, especially in the adolescent or maybe pediatric subgroup, sputum eosinophilia, which you had pioneered the use of, is probably more variable than in the adult population, and I'm wondering if that also extends to serum eosinophilia.

So the question would be stability of eosinophilia. And I guess maybe the slide that talks to this in some way would be -- I think it was slide 52. To kind of get to the issue at hand, looking at indication, in some ways this also addresses the "or" in that qualifying statement.

DR. ORTEGA: Sure.

DR. GEORAS: Eosinophils historical greater than 300 or greater than 150 at time of enrollment.

DR. ORTEGA: Slide up, please. So you're

referring to slide 52 that indeed accounts for the historical eosinophils in baseline less than 50.

So I'm going to address your question with data that we generated from our group of patients that participated in the 997 trial. Slide up, please.

We published this data earlier this year in the *Annals of ATS*, where we look at the patients who were on the placebo group, and we were precisely interested in the stability of the blood eosinophil as a biomarker, and whether we needed to have repeated measures to see if that level that we achieve changes with subsequent measurements.

If we look at the graph here, it represents two studies, the 997 on blue and the 588 on orange. In the horizontal axis, we have a number of blood samples used to predict subsequent eosinophil counts.

Now, what is important here, we are looking at the vertical axis, the percent of patients with an average above the 150 threshold, which is the group that is likely to receive benefit with

mepolizumab.

So when we look at one measurement, as illustrated here, we have 85 percent of the patients will stay above that level through the duration of the trial.

Then it would take a second measurement if you see there was no difference. It was still 85 percent. And the average of the three measurements was about 90 percent, and subsequently the average of four was about 92 percent, and the results were very much replicated in the second study.

Now, we don't have data in the real world. This is data, again, of patients who participated in the clinical trial.

MR. YANCEY: Can I ask Dr. Pavord to comment on that last piece? Because you asked about using eosinophilia as a biomarker and is it ready for community use.

DR. PAVORD: These are very valid comments and concerns and, of course, when using any biomarker in clinical practice, it's absolutely crucial that you understand the measurement

characteristics, and one of those crucial ones is within subject repeatability.

There is quite a lot of data -- I'm struggling to think of an adolescent-specific study -- in adults with airways disease. And one way of looking at repeatability is the intra-class correlation coefficient, which is a ratio within subject variability, which you want to be small, and between subject variability, which you want to be large, and the intra-class correlation coefficient is around 0.8 for blood eosinophil counts.

So I think it is comparable with other blood-based biomarkers that we routinely use in clinical practice, like blood sugar and serum cholesterol. But is very important that the clinician understands this marker. And clearly, a clinician would attach much more significance to a highly abnormal result than a borderline result, and I think clinicians are very familiar with that sort of thought process.

MR. YANCEY: In the clinical studies, some

patients were on oral glucocorticoids, correct, which are going to affect the eosinophil counts. Do you know if the utility of this biomarker is affected by the use of oral glucocorticoids or not?

MR. YANCEY: Dr. Ortega, would you like to take that question?

DR. ORTEGA: Yes. Indeed, we have looked at specifically the 575 trial, which was our steroid reduction trial. And if you remember, in the presentation of the baseline characteristics, I mentioned the point that actually the baseline blood eosinophil count is quite similar to the exacerbation studies. So there is still a quite valid biomarker despite those patients taking oral corticosteroids.

We know, in general, steroids are very good at affecting the level of eosinophils, but in general, the biomarker still is quite valid with thresholds that we identified. In fact, a little bit surprising for us was that the levels were quite similar between the two studies.

DR. SWENSON: We've come to the break time,

but we have a couple more people that I think should have a chance here, and I think we have time enough in the day to do that. But I would ask you to please keep it to just a clarifying question. We'll have time enough in the afternoon to really get into the larger issues.

Dr. Blake, you are next.

DR. BLAKE: Thank you. This is just a general question. We were told that about 3 percent of asthmatics have eosinophilic airway inflammation. What is the percent in adolescents, since we've heard that it was lower in adolescence?

I'm trying to get at like what is the total number of adolescents that would be eligible for this drug in the U.S.

MR. YANCEY: It's very difficult to find precise data in this space. As you can imagine, this is a moving field of science and medicine.

We've been able to look across some managed-care databases. We're able to look at adolescents aged 12 to 17, and then look at their medication use.

So recall that the directed use of this medicine would be for patients who are on optimized doses of steroids, as well as at least one additional controller and having exacerbations.

So when we look across large databases, we see that of the adolescent population, so of all asthma patients 12 to 17, this group is in the 1 to 2 percent of that population, so it's quite small.

DR. BLAKE: One other question. In terms of immunogenicity, would you be recommending that the antidrug antibody assay be done after treatment starts?

MR. YANCEY: Given the very low rate of ADA responses, the fact that over 50 percent of patients only had one positive ADA, it is not a current recommendation. We believe it would be a requirement for the safe use of this medicine. We would continue those discussions in negotiations with the agency as we move through the review process.

DR. SWENSON: Dr. Raghu?

DR. RAGHU: Thanks very much. Ganesh Raghu

from University of Washington-Seattle. I have two specific questions. One is with the inclusion and exclusion criteria with reference to where eosinophilia is concerned, and the other one is the open-label extension.

So the first question is I recognize that the parasitic infestations, or at least a history of parasitic, was eliminated in terms of patients enrolled in this particular study. But because of the eosinophil, it's a major pivotal consideration, biological possibility. How well did you eliminate the parasitic infestations?

Then, also, I see that this was a global population, but you have not really included in all endemic areas that parasitic infestation is a consideration. And I'm concerned about the postmarketing aspect of this if it is approved, is how well it can be used in the parasitic infestation-associated eosinophilia.

So that is one question in terms of inclusion and exclusion criteria. The second question is with reference to the open-label

extension. How well was the reduction in the corticosteroids in the open label sustained if you have captured that data, as well as the decreased exacerbation in the patients who were originally on the placebo and then the open-label extension?

MR. YANCEY: I'm going to invite Dr. Leadbetter to come to the podium to address your first question, and I'll just try to close out question two.

So in the open-label extension studies, you have asked whether or not the OCS reduction can be maintained over that longer period of observation, as well as control of exacerbations, and we did not see any increase. In fact, we've seen a lowering of exacerbations, for example. So the durability of this clinical result has been demonstrated in those studies.

The other specific question, Bob, was around parasitic infestation. The question was around the inclusion/exclusion criteria, but I think perhaps a discussion around the full clinical context of that would be helpful.

DR. LEADBETTER: Thank you for your question. We did exclude individuals with known parasitic infections in the program largely because we didn't want the confound of eosinophilia from that infection to affect the interpretation of the efficacy and safety data.

There was one individual who was reported to have developed a parasitic infection during the trial, was treated, that resolved. However, there was no pathology, there was no laboratory test to confirm that that individual actually had had a parasitic infection.

So, again, we did exclude. We did not see, except for this one individual, incidents during the program that concerned us.

Our recommendation going forward has been that certainly if an individual has a parasitic infection before they are being treated with mepolizumab, that the parasitic infection should be treated, of course, before starting.

If an individual were happen to develop a parasitic infection during the treatment with

mepolizumab, our recommendation is that if they do not respond to standard parasitic treatment, then a temporary cessation of mepolizumab might be considered.

We have no direct evidence to suggest that mepolizumab should interfere with response to parasitic infections. And indeed, in animal models, when you look at them, parasitic infections can be cleared in the complete absence of eosinophils, and it does appear as though other immune mechanisms will kick in to respond to parasitic infections.

DR. RAGHU: How well did you eliminate the parasitic? Were you looking for antibodies for parasites? Because this could have been a random eosinophil count somewhere 10 months before the patient came into the trial. So it was simply based on a history that you had parasites, or how did you eliminate them?

DR. LEADBETTER: You are correct. It was simply based on history. We did have some trials in some high endemic areas, and I think we take

some comfort in the fact that we did not see a greater incidence of parasitic infections in those areas.

DR. SWENSON: Well, at this stage, we should take a 10-minute break, and I think these are questions that we can follow-up on in the remaining sessions.

So it is now 10:33 and I'd like to resume in 10 minutes at 10:43. Thanks.

(Whereupon, at 10:33 a.m., a recess was taken.)

DR. SWENSON: Welcome back, everyone. We will now proceed to the presentation by the FDA. Dr. Chaudhry, the podium is yours.

FDA Presentation - Sophia Chaudhry

DR. CHAUDHRY: Good morning. My name is Sofia Chaudhry. I am a medical officer and allergist in the Division of Pulmonary, Allergy, and Rheumatology Products. I would like to thank members of the advisory committee today for your presentation and preparation and attendance at this meeting today. We truly value your input and the

discussion of this application.

The goals of today's committee discussion have already been outlined for you earlier in Dr. Gilbert-McClain's introductory comments, and the sponsor has provided detailed presentations of the efficacy and safety data from this program.

As the agency does not have any major disagreements with the sponsor regarding the safety or efficacy analyses, the goal of the FDA presentations this morning are not to re-present the data, but rather to highlight aspects to help frame the committee's discussion today.

I will begin by providing a brief reminder of the mepolizumab clinical development program. Dr. Abugov, the agency's statistical reviewer, will then provide an overview of the efficacy from the statistical perspective.

This presentation will include additional analyses conducted by the agency to help address the question regarding the role of the eosinophils in guiding therapy in the severe asthma population. I will then return to the podium to provide a brief

overview of the safety data to help frame the risk/benefit discussion, as well as provide additional comments on the adequacy of the African-American and adolescent populations.

As you have already heard, mepolizumab is provided as a lyophilized powder for reconstitution and administration by a health care professional. The proposed dose and route for marketing is 100 milligrams subcutaneous every 4 weeks.

You have already heard the sponsor's presentation of the data supporting dose selection, as well as the division's concurrence with the selected dose in Dr. Gilbert-McClain's introductory comments this morning.

As the division concurs that the data support the proposed dose and route for marketing, the agency will not be providing any further presentation of the dose-ranging data.

Finally, as outlined in Dr. Gilbert-McClain's presentation, mepolizumab, if approved, should be directed to a targeted patient population with severe asthma who are uncontrolled

in spite of maximal controller therapy as add-on to other maintenance therapies. In addition, given the mechanism of action, it is anticipated that blood eosinophil levels are likely to play a role in directing therapy.

The next set of slides provides an overview of the mepolizumab development program. The initial asthma study conducted by GSK in 1999 will be referred to as study 6 in the agency's presentations. This lung function study in patients with moderate asthma, without further enrichment for eosinophilic inflammation or exacerbations, failed to demonstrate a benefit after 12 weeks of therapy.

Following publication of these results in 2007, two investigator-sponsored studies were conducted in a severe asthma population enriched for evidence of the eosinophilic inflammation. These studies provided data suggesting that mepolizumab may be efficacious in a more selective patient population.

GSK subsequently reinitiated its asthma

program and conducted study 97. The 52-week dose-ranging exacerbation study in patients with severe asthma, with a history of exacerbation and further enriched using multiple markers, the sponsor has identified as indicative of eosinophilic inflammation.

As you have heard, all of the mepolizumab doses in this study resulted in statistically significant improvements in exacerbation.

Building on these results, GSK subsequently conducted two additional efficacy studies in the severe asthma population using more refined criteria to enrich for eosinophilic inflammation. These included study 88, a second 32-week exacerbation study, and study 75, an oral corticosteroid reduction study.

The sponsor also initiated studies 61 and 66, which were two open-label safety extensions to provide longer-term data. Following positive results from the development program, GSK filed its BLA with the FDA in late 2014.

This slide outlines the study designs for

the pivotal efficacy studies identified by the division. I will not present the table in detail as you have already heard an overview of the trial designs in GSK's presentation this morning. Additional details on the enrichment criteria used by the sponsor will be detailed in the next slide.

But to summarize, you can see that study 6 was a randomized, double-blind, placebo-controlled, 12-week lung function study evaluating 2 doses of IV mepolizumab against placebo in a less severe asthma population. Studies 97 and 88 were exacerbation studies in a severe asthma population that was further enriched for evidence of eosinophilic inflammation.

As noted earlier this morning, the division acknowledges the exacerbation definition used in these studies as a robust and clinically meaningful assessment.

Study 75 was a 24-week steroid reduction study evaluating the to-be-marketed dose, 100 milligram subcutaneous, against placebo, and provides additional efficacy support for

mepolizumab.

Now that I have outlined the designs of the pivotal efficacy trials, I will move on to an overview of the population enrichment strategy. You can see that study 6 allowed for enrollment of a broader, less severe asthma population. While all patients were on background ICS therapy, patients were not taking an additional controller therapy. There was also no requirement for an exacerbation history and no specific enrichment for evidence of eosinophilic inflammation.

Studies 97, 88 and 75 targeted a more severe population and required background asthma therapy with high-dose ICS plus an additional controller, with or without oral corticosteroids.

For the exacerbation studies, studies 97 and 88, subjects were required to have a history of two exacerbations in the prior year. However, this was not a requirement for study 75.

Regarding the eosinophilic enrichment criteria, for study 97, subjects could qualify for study entry by meeting any one of four criteria,

while studies 88 and 75 used criteria that were further refined and based on peripheral blood eosinophil levels.

For these studies, patients were required to have a screening blood eosinophil count greater than or equal to 150 or historical elevation greater than 300 in the prior year.

While the previous slide provides an overview of the criteria used by the sponsor to enroll its targeted patient population, this slide provides an overview of the actual demographic data for selected disease characteristics from each of these studies.

You can see in the first line that study 6 enrolled, on average, a younger patient population, with a mean age of 36 compared to 50 for the severe asthma program. While asthma duration data were not available for study 6, the severe asthma population had, on average, asthma for around 20 years.

As expected, based on the enrollment criteria, the average ICS dose was lower in

study 6. Notably, patients enrolled in the severe asthma program had, on average, over 3 exacerbations in the prior year despite standard of care background therapy.

Finally, while specifically enriched for specific eosinophil parameters, you can see that patients in study 6 had a similar mean peripheral blood eosinophil count obtained around the time of treatment initiation, as the severe asthma studies, with a wide range of counts seen across the studies.

Finally, as Dr. Gilbert-McClain mentioned in her introductory comments, in addition to a discussion of the intended patient population, the agency is asking the panel to discuss the adequacy of the subgroup data for the African-American population and adolescents.

This slide outlines the number of patients in these specific subgroups both for the global asthma development program as a whole, which includes the United States, as well as a percentage of the enrolled population from the U.S.

For the global program in its entirety, you can see that a total of 39 patients of African heritage were enrolled across the three severe asthma studies, which accounts for less than 4 percent of any individual study.

The proportion of African-Americans enrolled from the U.S. centers for the exacerbation studies are more reflective of the U.S. population, with study 97 enrolling 28 percent African-Americans and study 88 enrolling 21 percent. However, the overall numbers are still low since subjects from the U.S. accounted for only about 10 to 15 percent of the entire clinical development program.

For adolescents, a total of 28 patients were enrolled in the program, with 25 of these patients enrolled in study 88. The sponsor is currently proposing an indication in patients 12 years of age and older. The size of these databases will be important to keep in mind throughout the remainder of the agency's presentations.

I will now turn the podium over to Dr. Abugov to discuss the agency's statistical

review of efficacy.

FDA Presentation - Robert Abugov

DR. ABUGOV: Thank you, Dr. Chaudhry.

I'm Robert Abugov, the statistical reviewer for this submission. In this presentation, I will provide an overview of the studies and the endpoints we'll examine, and then summarize results regarding the effect of mepolizumab on exacerbation rate, ability to reduce oral steroids, and change from baseline FEV1.

We will see that this submission provides clear evidence of efficacy for reduction of exacerbation rate, as well as significant reductions in oral steroid use. Less clear are effects on change from baseline FEV1.

We will then examine the impact of the eosinophil count on mean exacerbation rates and see that there is an association between blood eosinophil count and treatment effect. Finally, subgroup analyses regarding effects of age, gender, race, and region will be provided, and then we will wrap things up with a summary.

Effects of mepolizumab on change from baseline FEV1 will be discussed in four studies, on exacerbation rate in two studies, and on ability to reduce oral steroids with minimal impact on asthma symptoms in a single study.

Let's now get to the results. We'll start with the primary endpoint for studies 97 and 88, the exacerbation rate. Throughout this presentation, exacerbation rates will be analyzed and described using risk ratios. These fractions are expressed as the event rate for the mepolizumab group divided by the event rate for the placebo group; so that a fraction smaller than 1 indicates a reduction in exacerbation rates for mepolizumab relative to placebo.

It is important to note that interpretation of a risk ratio depends critically on the rate of exacerbations in the placebo group. For example, in the table at the bottom of this slide, the risk ratio is constant and equal to one-half, indicating that exacerbation rate for the treatment group is one-half that for the placebo group.

However, the benefit of treatment in reduced number of exacerbations per patient year varies widely. When the event rate of interest is more common in the placebo group, the benefit of treatment is larger.

For example, if there is an average of 5 events per year in the placebo, the risk ratio of one-half represents an average reduction of 2.5 events per year. However, when the event of interest is less frequent in the placebo group, the reduction of one-half corresponds to a lower number of events avoided per patient with treatment.

In the studies we discuss today, the events in the placebo group are not always common and the risk ratio should be interpreted in this context. Seemingly large reductions on the ratio scale may be misleading. The number of events avoided expressed on the risk difference scale should be considered.

This table considers exacerbations defined according to all of the exacerbation criteria in the sponsor's protocol, including increases in the

use of steroids, hospitalization, and/or emergency department visits.

In all other slides I'll present, the 95 percent confidence intervals are unadjusted for multiplicity, with implied p-values valid only in confirmatory analyses.

The risk ratios for each of the 3 doses suggest that mepolizumab reduces the rate of exacerbations by approximately one-half. These results are statistically significant, as shown by the p-values. On an absolute scale, patients treated with mepolizumab rather than placebo avoided approximately one exacerbation per year.

As a final note, you can see that treatment effect did not appear to be impacted by dose.

For exacerbations requiring hospitalizations and/or emergency department visits, the risk ratios suggest that mepolizumab reduced the rate by approximately one-half, a reduction similar to that shown in the previous slide for exacerbations including increases in steroid dose.

For hospitalization plus emergency

department visits, this corresponds to an average reduction of approximately 0.2 events per patient-year with treatment. For exacerbations involving hospitalization only, the reduction was approximately 0.1 events per patient-year.

Effects for the exacerbations in this slide were in the direction consistent with effectiveness, but after applying corrections for multiplicity, none of the effects were statistically significant. Similarly, for study 88, regardless of the criteria used for exacerbations, mepolizumab reduced the rate of exacerbations by approximately one-half.

For exacerbations associated with all criteria, mepolizumab reduced the absolute exacerbation rate by slightly less than one event per patient-year.

For exacerbations defined using criteria limited to hospitalization and/or emergency department visits, mepolizumab reduced the average absolute exacerbation rate by approximately 0.1 event per patient-year.

After applying a correction for multiplicity, only the 100-milligram subQ dose for hospitalization and emergency department visits was statistically significantly different from placebo.

As might be expected from study 97 and earlier PD studies, treatment effect did not appear to be impacted by dose.

So to summarize, in patients with severe asthma and eosinophilic inflammation, mepolizumab is effective for reducing exacerbations. With treatment, point estimates of the exacerbation rate, including all criteria, were reduced by approximately half on the rate ratio scale and by approximately one event per patient year on an absolute scale.

Let's now examine the effects of mepolizumab on ability to reduce oral steroids. As you'll recall, in study 75, OCS reduction was examined by imposing tapering on patients and backing off that tapering if the patient experienced worsening of asthma symptoms.

The results here categorize patients during

weeks 20 to 24 according to percent reduction achieved from initial OCS maintenance dose. Patients taking mepolizumab achieved significantly higher reductions in OCS dose than those on placebo. The odds ratio was 2.4 with a p-value of .009.

So we have a confirmatory study which clearly demonstrates OCS reduction. Let's now consider one last endpoint.

Submissions for pulmonary drugs typically focus on change in lung function. However, as you have seen, the mepolizumab development program focused on exacerbation rate or OCS reduction as primary endpoints.

In the analysis hierarchies, change from baseline FEV1 was low or not even included, and as such, many of the analyses presented on this slide are not considered confirmatory. Among the trials, change from baseline FEV1 was examined as a confirmatory analysis only in study 97, and in that study the effect was not significant.

Let's now move on to consider potential

effect modifiers. Here we address the possibility of prescribing mepolizumab only to asthma patients who have particular characteristics. To provide such personalized medicine, we need to understand which patient characteristics, if any, modify the effects of treatment.

First, we'll cover a bit of statistical methodology regarding evaluation of effect modifiers, then we'll detail exploratory analyses by the sponsor which suggest that blood eosinophil count and prior exacerbation rate are measurable characteristics, which may modify treatment effect. Finally, we'll provide some FDA-defined analyses to test the sponsor's assertions.

Regarding methodology, here is a typical example for which there is no effect modification. The potential biomarker, in this case, screening blood eosinophil count, is represented on the horizontal axis. Study outcome, or in this case, exacerbation rate, is shown on the vertical axis. The upper line represents the placebo group and the lower line the treatment group.

In this example, the lines are parallel and, therefore, the treatment effect, the difference between treatment and placebo, does not depend on the value of the potential biomarker. This trait is not an effect modifier.

In this hypothetical example, the trait on the X-axis is associated with changes in treatment effect, and the trait is, therefore, an effect modifier. The positive association between the trait and treatment effect is driven by non-parallel outcome lines, with a difference between placebo and treatment becoming larger at higher values of the trait.

Mathematically then, a trait modifies treatment effect when the slopes of outcome with respect to that trait differ between treatments. We evaluate effect modification, the difference between slopes, by examining the statistically significance of the interaction between treatment and the effect modifier.

This slide illustrates the sequence in which studies 97 and 88 were designed. First, study 97

enrolled severe asthma patients enriched by criteria, which the sponsor believed to be associated with the eosinophilic inflammation, as listed in the upper box.

The sponsor explored study 97 for effect modifiers, and then used the results to limit enrollment in subsequent study 88 to patients for whom treatment effects were expected to be large, as indicated in the lower box on this slide.

In analyzing the data from study 97, the sponsor considered a large number of potential effect modifiers, as indicated in the upper box in the slide. These explorations tested the interaction of each covariate with treatment.

Nominal significance was seen for interactions of treatment with baseline blood eosinophil count and number of exacerbations in the year prior to treatment, indicating that these factors may be effect modifiers for mepolizumab. The sponsor, therefore, decided to use these two factors as enrichment criteria for patient enrollment in study 88.

FDA analyses used in the remainder of this presentation largely corroborate the sponsor's analyses regarding blood eosinophil counts and prior exacerbations. Our analyses examine interactions by adding to the primary analysis model the potential outcome modifier, or effect modifier, and its interaction with treatment, comparing outcomes between placebo and the average of the mepolizumab doses.

To avoid wasting statistical power, we do not impose categories on continuous or integer variables while testing for effect modification. Instead, we simply used the continuous or integer variables without any reliance on cut points between imposed categories.

We graphically present exacerbation results by categorizing effect modifiers, but only as a visual aid and only to help understand the meaning of interaction terms.

We'll begin with study 97. Let's look at the distribution of blood eosinophil count and prior exacerbation rate among enrolled patients at

screening. In study 97, blood screening the eosinophil counts ranged from zero to about 3,000. Roughly half of enrolled patients had screening blood eosinophils greater than 300 per microliter. Because the distribution was skewed to the right, I used a log count in the analyses.

Similarly, number of exacerbations in prior year were skewed to the right, and so they were logged for the analyses. Most enrolled patients, approximately 70 percent, had 2 to 4 exacerbations in the prior year.

As evidenced by a nominally significant p-value of 0.4 for the interaction, shown in the bottom right corner of this slide, there was a positive association between reductions in exacerbation rate and screening blood eosinophil count.

The forest plot is for descriptive purposes. It illustrates the effect of each mepolizumab arm relative to placebo across four categories of eosinophil count. Each group of three lines represents the different dose arms of mepolizumab.

From top to bottom of the graph, screening blood eosinophil count increases, with counts less than 150 per microliter at the top followed by 150 to 300, then 300 to 500, and, finally, at the bottom, for patients with more than 500 eosinophils per microliter.

The forest plots show effects which are lower at the top of the graph for low eosinophil counts and which are higher at the bottom of the graph for patients with high blood eosinophil counts.

In study 97, reductions in exacerbation rate with mepolizumab treatment were affected by the number of exacerbations in the year prior to enrollment, with a nominal p-value of .02.

In the graph, we have effects of the 3 treatments compared to placebo, at the top for 2 exacerbations in the prior year, followed in the middle for 3, and on the bottom for 4 or more exacerbations in the prior year. There is evidence for a larger treatment effect when patients experienced more than 2 exacerbations in the prior

year.

Without control of type 1 error, we also looked at the possibility that other enrollment criteria used for study 97 to gauge eosinophilic inflammation may also provide important effect modification for mepolizumab.

First, we consider whether treatment effect from mepolizumab varies according to exhaled nitric oxide level. The nominal p-value for the test of treatment by nitric oxide level is 0.5 and does not indicate any effect modification.

Similarly, the nominal p-value for the test of treatment by loss of control category is 0.2, not significant, and the forest plot does not suggest any significant differences in treatment effect according to whether or not patients did or did not experience loss of control when screening OCS doses were reduced.

Finally, for study 97, there was no clear trend of effect modification for screening sputum eosinophils. The nominal p-value for the test of interaction was 0.5.

So in summary, exploratory analyses from study 97 suggested incorporating enrollment restrictions in study 88 based on screening blood eosinophil count and number of exacerbations in the year prior to screening.

Other variables indicative of eosinophilic inflammation used for screening in study 97 were examined but were not found to be promising as enrichment criteria for confirmatory study 88.

Let's now move on to see what happened in study 88.

Study 88 was designed with knowledge of the effect modifications observed in study 97, and it evaluated the effect of mepolizumab among patients enrolled with restrictions on blood eosinophil count and prior exacerbations.

In study 88, screening blood eosinophil counts ranged from zero to 2500, with a distribution again skewed to the right. Roughly half of the enrolled patients had screening blood eosinophils greater than 350 per microliter. Exacerbations in the prior year were again skewed

to the right. Most enrolled patients, almost 70 percent, had 2 to 4 exacerbations in the prior year.

The interaction between screening blood eosinophil count and treatment was nominally significant, with a p-value of 0.03. The graph suggests a trend in which higher blood eosinophil counts are associated with larger treatment effects.

For reduction in exacerbation rate as a function of prior exacerbations, there was no obvious trend, with a nominal p-value for the interaction equal to .7. It seems possible that a significant effect modification would have been seen for exacerbation history if a broader population had been examined rather than just patients with 2 or more exacerbations in the prior year.

So in summary, exploratory analyses from study 97 suggested incorporating enrollment restrictions into study 88 based on screening blood eosinophil count and number of exacerbations in

year prior to screening.

Analyses from study 88 show a positive association between eosinophil count and mepolizumab treatment effect, but there was no suggestion of a statistically significant association between treatment effect and number of exacerbations in the year prior to study conduct. This may be at least partially a result of the fact that patients with zero or 1 exacerbations in the prior year were excluded from the trial.

Let's now move on to effect of other subgroups on the efficacy of mepolizumab, such as age, gender, treatment, race, region, and ethnicity. For these analyses, we again averaged the mepolizumab doses and compared to placebo.

For study 97, benefits of mepolizumab in terms of exacerbation rate were seen regardless of gender, age, race, or ethnicity. However, because of limited enrollment, no assessments were available for patients aged 12 to 17.

In study 88, there was a suggestion of limited or even negative efficacy for mepolizumab

among patients of African descent. However, the confidence interval for those patients is extremely wide and a beneficial effect cannot be ruled out.

In study 75, positive effects and log odds ratios were seen for all subclasses. However, as in study 97, there was no comparison available for patients 12 to 17 years old because few such patients were enrolled in this study.

In study 97, mepolizumab reduced exacerbation rate regardless of region. We also see reductions in exacerbation rate regardless of region in study 88.

We can now wrap this up with a summary and conclusions. There was clear evidence that mepolizumab reduced the rate of exacerbations relative to placebo, and such reductions in exacerbation rate were greater among patients with high blood eosinophil counts. There was also evidence from a single study that mepolizumab facilitates reductions in OCS use with minimal impact to asthma symptoms.

No statistically significant effects of

mepolizumab were seen for change for baseline FEV1. And finally, although no differences between subgroups were seen for efficacy, available data was limited for adolescents and patients of African descent.

Thank you for your attention. I'll now turn the podium back over to Dr. Chaudhry.

FDA Presentation - Sofia Chaudhry

DR. CHAUDHRY: I will now complete the agency's presentations this morning.

As Dr. Gilbert-McClain outlined earlier this morning, in the discussion portion of this meeting, you will be asked to discuss the available efficacy and safety data for this product and ultimately vote on whether the risk/benefit supports approval.

You have already heard a detailed presentation from GSK on the safety data. So for my presentation, I will only provide a brief summary as a reminder for the requested risk/benefit discussion.

I will then summarize the efficacy data with a specific focus on the questions you are asked to

discuss, including the intended patient population, as well as the adequacy of the available African-American and adolescent data.

The safety review for this program largely relies on data from the placebo-controlled severe asthma safety database, which includes data from studies 97, 88 and 75. In this database, there were 915 severe asthma patients exposed to mepolizumab, 387 of whom were exposed for at least a year.

The open-label safety studies provide additional data for greater than one year in 836 severe asthma patients with a median exposure of about 20 months in study 66 and 12 months in study 61. While smaller than more recent asthma development programs, the division finds the database adequate for review given the limited number of patients with severe asthma.

This slide summarizes the deaths seen in the severe asthma program. A total of 8 have been reported across the program, with numbers generally balanced across treatment arms. A larger than

expected number of respiratory-related deaths are seen in the program. However, again, events are balanced across arms, including placebo, which suggests against a treatment-related effect. Rather, this may be indicative of the underlying severity of the patient population.

Reassuringly, as you will see on the next slide, respiratory-related serious adverse events favor active treatment, which is not surprising given the treatment effect on exacerbations demonstrated in the program.

Moving on to the nonfatal serious adverse events, overall, mepolizumab-treated patients consistently had fewer SAEs than placebo-treated subjects. This largely appears driven by a decreased number of asthma SAEs, which is consistent with the efficacy of the product, efficacy the product demonstrated in reducing exacerbations.

As noted in the briefing package, cardiovascular safety was identified by the sponsor as an adverse event of special interest based on an

imbalance in cardiovascular SAEs seen in study 97. You can see in this table of the placebo-controlled severe asthma database that the overall number of events are small, and when the data are grouped by ischemic versus arrhythmic events, the numbers decrease even further, making it difficult to conclude that there is any treatment-related effect.

Importantly, an increased number of events is not seen for the 100-milligram subcutaneous dose proposed for marketing.

Additional adverse events of special interest include local site reactions, systemic hypersensitivity, including anaphylaxis, malignancy, and opportunistic infections. An imbalance is seen in local site reactions.

However, no consistent treatment-related effect is seen for other adverse events of special interest, including malignancy-related and opportunistic infections, which are a theoretical concern given the mechanism of action of mepolizumab, although the limited size and duration

of the database and the exclusion of patients at risk for parasitic disease should be kept in mind when considering these data.

Finally, to complete the agency's summary of the safety data, this slide presents the most common adverse events derived from the pooled data from study 75 and the first 24 weeks of study 88. You can see that headache was the most frequently occurring event followed by injection site reactions.

Now that I have completed the brief overview of safety, I will move on to a discussion of the efficacy data with a specific focus on the targeted patient population, as well as a discussion of the data from the African-American population and adolescents.

As you have heard throughout the morning, this program demonstrated consistent replicate statistically significant decreases in exacerbations of about one per year on top of background standard of care therapy in the two asthma exacerbation studies in severe asthmatics.

Additional supplemental data supporting efficacy of the product is seen in a small, single oral corticosteroid reduction study in which mepolizumab treatment resulted in the ability to titrate to a lower corticosteroid dose without loss of asthma control.

While not a primary assessment in this program, it is useful in any asthma program to consider the available lung function data. As you have already heard, study 6 failed to demonstrate any improvement in lung function in a less severe population after 12 weeks of therapy despite a reduction in eosinophil counts.

Study 97 also failed to demonstrate a consistent numeric improvement in lung function over placebo, although a 61 mL improvement is seen at the end of the study, while studies 88 and 75 demonstrate improvements of about 100 mLs compared to placebo by the end of each study.

It is worth noting that these data were obtained while patients were being maintained on background standard of care therapy, including

maximal bronchodilator use.

The difference in response between studies 97, 88, and 75 remains unclear, but as can be seen on the time curves included in the briefing package, the placebo arms behaved differently in each of these studies.

Now that I have summarized the safety and efficacy data, I will move on to a discussion of the targeted patient population.

As I noted in my earlier presentation, the patient program for mepolizumab has evolved over the course of its development. The initial study failed to demonstrate a lung function benefit in a broader, less severe population despite a reduction in the eosinophil counts, although it is worth noting that the study was of shorter duration and there was no formal eosinophilic or exacerbation enrichment or formal exacerbation evaluation.

These studies are in contrast to the positive efficacy results seen in studies 97 and 88, whose study populations roughly correspond to the white circle depicted in this figure, which is

believed to represent less than 5 percent of the asthma population.

The clinical characteristics for this group are outlined on the right of the slide. This highly select population included subjects with a history of exacerbations despite maximal standard of care therapy who also met specific eosinophil enrichment criteria.

We anticipate that this is the targeted patient population that will be captured in the product labeling, as we have positive efficacy and safety data to support use in this population. Use outside of this population does not appear to be supported at this time, as the program lacks data demonstrating efficacy and safety in a broader asthma population.

With regard to the role of the eosinophil count, as you saw in Dr. Abugov's presentation, a positive interaction test is seen between mepolizumab and exacerbation reduction. In other words, an increased treatment effect is seen with increasing blood eosinophil levels obtained around

the time of treatment initiation.

While multiple forest plots were presented in Dr. Abugov's presentation, I have presented the forest plot from study 88 using the sponsor's threshold values of 150 and 300 on this slide as a reminder. You will note the wide confidence intervals seen with counts less than 150, which are likely influenced by the relatively small amount of data in this program for this group of patients.

As noted by Dr. Gilbert-McClain in her introductory comments, we are asking the panel to discuss the role of peripheral blood eosinophil levels in selecting appropriate patients for treatment.

The agency is requesting the panel's input on how the eosinophil data can be used by the practicing community to select appropriate patients so that therapy is not inappropriately withheld from patients with severe disease who have limited treatment options, while, at the same time, therapy is not inappropriately given to patients unlikely to benefit.

Should the product be approved, your insights today will assist the agency and GSK in working together to write an informative product label.

In addition to the role that asthma severity and eosinophils play in selecting appropriate patients for therapy, the panel is also being asked to discuss the available data we have for the African-American subgroup given the increased morbidity seen with these patients.

On this slide, you can see that the point estimate falls in the appropriate direction in study 97, but in the opposite direction for study 88. However, wide confidence intervals are seen for both, indicating a high level of uncertainty with these data likely due to the limited data we have from this population in the development program.

Finally, the panel is also asked to discuss the adequacy of the pediatric data and provide its recommendations on whether the data are sufficient to support approval in this age group. Integral to

this discussion will be a consideration of the amount of available data, the relevance of the evaluated patient population to the pediatric population, and whether mepolizumab treatment is anticipated to result in similar treatment effects in younger patients.

As a reminder, the overall population studied in this program had a long history of asthma, on average, 19 to 20 years, and a mean age of about 50. The data we do have for the pediatric population is primarily drawn from 25 patients in study 88, with the point estimate trending in the appropriate direction as the adult population. However, you can see the data have wide confidence intervals, again, indicating a high level of uncertainty.

So to briefly summarize, you've heard this morning that mepolizumab demonstrates a consistent statistically significant decrease in exacerbations in the highly select patient population evaluated in its severe asthma program. You further heard that no major safety signals have been identified

to date, although lingering concerns remain regarding the risk of parasitic disease, as these patients were excluded from study.

Finally, beyond a discussion of the risk/benefit in the overall targeted patient population, you have heard the agency's concerns regarding the adequacy of the data in certain subgroups, specifically African-Americans and adolescents.

I'd like to thank the committee for its attendance at this meeting today. We look forward to hearing your discussion. And I will turn the podium back to the chair. Dr. Swenson?

Clarifying Questions to Presenters

DR. SWENSON: Thank you. We will now open up discussion with clarifying questions to the agency. Dr. Blake?

DR. BLAKE: I know that you said -- this is from the talk on the statistical analysis -- that you didn't do any categorization of the continuous or integer variables. But when would you do a receiver operating curve analysis to look at this?

DR. ABUGOV: No receiver operating curve was done for these studies.

DR. BLAKE: It was not? I mean, but would you consider doing that to look at the efficiency of the model?

DR. ABUGOV: It's commonly done when we're trying to evaluate diagnostics when we have clear categorizations. One question we are trying to determine among ourselves is whether categorizations are necessary or desirable and how to do the labeling for that.

DR. SWENSON: Dr. Morrato?

DR. MORRATO: Thank you. This is Elaine Morrato. My question regarded the statistical review, as well, and I wanted to hear the FDA's thoughts around the independent contribution of the historical eosinophil value, and I will tell you why.

I'm trying to piece together information that's in the sponsor's briefing, as well as in data that you have provided. So I found your 997-only analysis very informative and useful. And

if I look at what the sponsor has said, they say only 13 percent of those in the intent-to-treat met the historical eosinophil requirement only. So it's a small fraction.

They do present some data looking at relative risk of only those that had the historical information. That is different than what we were presented today, which could have included those that had baseline, as well. They show directional relative risk, but it does overlap with the confidence interval.

Then I noticed in your analyses -- or overlap with 1, non-significance. I noticed in your analyses we didn't -- I was wondering if you had comparable kind of figures in which you were looking at effect modifiers where you're looking at this historical value.

As this gets rolled out into practice, you want to minimize burden, you want to increase clarity. And I'm just looking at what is the evidence to say we should have this historical criteria, as well as the baseline. I hope that

makes sense.

DR. DAVI: So I'll try to see if we understand your question first. Are you essentially asking us if we have a forest plot of the patients who were enrolled because they have a historical value that qualified them and did not have a screening value that qualified them?

DR. MORRATO: Right, such that it would justify that there is value in that measure alone.

DR. DAVI: I regret we don't have that information.

DR. MORRATO: Do you have any thoughts? Since you've had a lot of consideration around how to best target the patient population, have you -- it seems the historical one, as a carryover with that, was a criteria used originally in 997, and in their modeling, you're saying it was seen in some level of effect modification, so it carried through.

I'm just trying to understand the added value of both measures.

DR. DAVI: I think the only thing I can

offer you is the baseline histograms of the blood eosinophil count at enrollment. And you can see the proportion of patients that were lower than the 150 threshold there. But your point is well taken, and we will explore those kinds of things.

DR. SWENSON: I wonder if the sponsor has any comments to that question, any insights that you could provide.

MR. YANCEY: So your question around the historical value -- and you pointed out that 13 percent of patients were listed as having historical without.

If we look at the data from the two exacerbation studies, if you look at the patients who have an historical value, firstly, it has to be available in the chart, so there is a limitation to that.

If we look at those patients who had a chart history and they had the 300, they are highly overlapping, 76 percent of those patients also had a baseline level of 150. So if you look back at the response, we presented data that looked at the

historical only without the 150, representing a 33 percent reduction in exacerbations, which is a very clinically relevant reduction. If we look at just patients who had 300 and you allow for the overlap, then those reductions are around 50 percent.

DR. MORRATO: Are you referring to slide A-53?

MR. YANCEY: Can we put up A-53, please? Yes. It's coming up in just a moment.

So what's illustrated on this particular slide are patients who met the historical independent of whether they did or did not meet the 100. So if you had an historical value, you had the 51 and 49 percent, so I just said approximately a 50 percent reduction.

If you have the baseline value, you may also have, in this particular plot, historical value. It's inclusive of both those with and without. And that means that you would see a 54 and 53 percent reduction.

DR. MORRATO: So it's a combination of met only and -- all right, because the Ns add up to

more than the Ns in the trial.

MR. YANCEY: That is because, again, you are taking both groups.

DR. MORRATO: Right. I understand that. It's a little unclear --

MR. YANCEY: This is a situation that the clinician will see in the field.

DR. MORRATO: Right. I think it needs to be very clear whether it's historical only, baseline only, or combination, because this doesn't imply that.

What's missing from this, I agree that the reduction percent is relevant, but in table 19 in the sponsor's document, when you present it in relative risk terms, then the historical only, still meaningful reduction. It's a 0.67 relative risk, but now the confidence intervals are overlapping with 1. So that is a very different interpretation than saying look how it's all very strong and consistent.

MR. YANCEY: I appreciate the point that you're making. I would just also add that as we

begin to look at various subgroups and look at smaller groups, those confidence intervals will always expand.

DR. MORRATO: I guess my point is what is GSK's point of view on the independent contribution of using the historical, recognizing it's a small percent. It's going to be a burden to roll this out to practices and say think about this, this and this. So what is the added value, in your point of view?

MR. YANCEY: So we believe the added value exists. We think it's providing a highly replicated -- and the clinicians will understand exactly what this means, because you are saying it's actually quite small. It's quite small if you say historical without the 150.

The fact is when you use the historical, most patients will, in fact, be above the 150. So it's actually quite a large group when you put those two together.

DR. MORRATO: Just, say -- take a baseline value and base it on that. That's an easy -- and

then the other information is useful, but -- okay. I'm beyond my clarifying.

MR. YANCEY: Again, we believe it's relevant, and we've tried to demonstrate also the stability of the eosinophil over time.

DR. SWENSON: Dr. Connett?

DR. CONNETT: Thanks. John Connett. The dosing schedule for this treatment is unusual. It's every 4 weeks subcutaneous. I think that is what is being recommended.

I'm wondering what the justification for that was. I'm also wondering whether the exacerbations that occur in the people that are taking the drug tend to occur toward the end of those 4-week cycles or at least in the latter half or last week of those 4-week cycles. And that's a question I think both for FDA analysts and maybe for the company, as well.

DR. SWENSON: Why don't we have the agency answer that first and then the sponsor.

DR. DAVI: I'm sorry. Could you repeat the question, please?

DR. CONNETT: There's a 4-week cycle of treatment. Every 4 weeks a patient gets subcutaneous injection. I'm also a little bit curious that that has to be done in a clinical center. But the pattern of exacerbations in people that are getting the active drug, do the exacerbations tend to occur toward the end of the 4-week cycle?

DR. CHAUDHRY: Sofia Chaudhry, FDA. So I'm not aware of any data where we know whether these exacerbations are occurring at the latter half of the dosing interval. I believe the dosing interval was mainly based off of pharmacodynamic data that we have regarding the reduction in blood eosinophil counts. But I'll look to GSK to clarify.

DR. ORTEGA: So the question is related to the interval of this treatment, which is every 4 weeks. That has to do with the also half-life of this monoclonal. It's about 21 days. So we have sustained effect on the pharmacodynamic inhibition of blood eosinophils that remain throughout that 4-week period. Therefore, our data is certainly

supported by the concept of the period effect seen.

DR. CONNETT: So you're saying the half-life is about 21 days.

DR. ORTEGA: Correct.

DR. SWENSON: Dr. Evans?

DR. EVANS: Clearly, the concern about parasitic infections has been raised both in terms of raising eosinophil counts and inappropriately enrolling people, as well as in subsequent ability to fight those infections. But I note in the data that has been provided by the agency that zoster episodes were notably elevated in the treatment group, but really haven't been discussed.

Is there any additional signal to suggest any difficulties with antiviral defense or zoster in particular?

DR. CHAUDHRY: You are correct. I did note that there was an imbalance in the herpes zoster infections that was seen both in the severe asthma program, and it has also been seen for other indications. But those data are largely confounded by the use of chronic oral corticosteroids across

both patient populations, so it's hard to really truly tease out the data.

There was no other signal in terms of viral infections or bacterial infections that I was concerned about.

DR. SWENSON: Dr. Georas?

DR. GEORAS: I had two questions. One was for, I guess, FDA perspective on the role of lung function testing in determining an indication for the drug. I take care of some severe asthma patient whose lung function is in the normal range, who might even not have bronchodilator reversibility, actually yet have frequent exacerbations.

So I guess the question would be the FDA's perspective on lung function testing given that an FEV1 of less than 80 percent, I think, was a requirement for entry into the pivotal studies.

DR. CHAUDHRY: Sofia Chaudhry, FDA. We're not viewing this drug as a bronchodilator, per se, and actually when we start looking at how we indicate asthma drugs in general, we generally

don't put specific criteria regarding lung function requirement. We leave that up to the clinician's judgment and whether they believe the patient would benefit or not with an underlying history of asthma.

DR. GEORAS: Can I ask a question for the sponsor? This almost follows-up some of the questions earlier. Would it be possible to present -- and if you don't have the data now, maybe after the break -- a table showing the reduction in exacerbation rate based on the historical versus baseline values?

I think I'm trying to infer if we do a two-by-two box, yes or no. I think we could probably characterize that just looking at slides 52 and 53. But I'm wondering if you could either present that now or after the break.

MR. YANCEY: We'll take that after the break.

DR. SWENSON: Dr. Raghu?

DR. RAGHU: My question is to Robert. It's mainly a comment. To me, as a non-statistician,

but a clinician trying to understand statistics, there is a clear-cut reduction in the exacerbation rate. Is it not statistically significant? Because I couldn't help noticing that you kept saying "suggestion" in the decreased exacerbation rate, and, to me, there is a concern. When there is a clear statistical significance, why are you using the word "suggestion"? So it's a matter of clarity for myself.

DR. ABUGOV: I think I used the word "suggestion" when I was talking about the trends in effectiveness with respect to eosinophil count. And the reason I use "suggestion" is because it's a post hoc analysis. As you know, statisticians are very picky about preplanned versus post hoc analysis.

DR. RAGHU: I understand. That is the reason I brought it up, because I thought you mentioned it when you were referring to the exacerbation rate, which is an important aspect here in the efficacy endpoint. So it may simply be an incidental slip of the word, so I just wanted to

clarify that for myself.

DR. ABUGOV: Yes. Except for analysis of trends, if I did use "suggestion," it was probably a misnomer from my conclusions.

DR. RAGHU: That's okay. The other question or comment is about the historical eosinophil count. Clearly, it is going to be an important aspect in the making of which patient population is going to respond.

Do you or the sponsor have any feeling of when this historical eosinophil count of 300 were -- is it closer to the inclusion or enrollment to the study or it could be anytime, any subgroup?

DR. ABUGOV: No. I just had a thought about how to show that. If I could bring up slide 24 from my presentation?

If you look at patients less than 150 per microliter -- let's go to -- not true for this study -- slide 34, please. There we go.

Given the inclusion criteria, the only way patients would get into study 88 with less than 150 eosinophils per microliter at screening would be if

they had 300 eosinophils per microliter in the past year. So you can see that there's very little evidence for an effect there.

DR. RAGHU: Thank you.

DR. SWENSON: Dr. Au?

DR. AU: Thank you. Maybe I missed it, but I was wondering if there was actually data on discontinuation of drug. I don't think I recall seeing any data on discontinuation relative to placebo.

Then as kind of a semi-tangentially-related follow-up, I'm actually wondering whether or not there are thoughts about as adolescents of a particular age, whether or not they will actually be able to come off the drug, and what the experience has been with people coming off drug and whether or not they are having increased exacerbations or any other kind of effects. Thanks.

DR. CHAUDHRY: You're correct. We didn't present specifically any data on drug-related withdrawal, but no major imbalances were seen

between the treatment groups.

Regarding adolescents and the ability to come off study drug, I think that you very eloquently brought in part of the question that we are asking. We are not aware of any data of how patients would be able to come off study drug, and that's particularly relevant when you're looking at a 12-year-old who might be looking at decades of treatment.

DR. AU: Can I ask one other follow-up to that? Is this drug then considered to be potentially lifelong therapy?

DR. CHAUDHRY: I don't know that I would be able to answer that. I suspect if you see a benefit as a clinician, I would have a hard time taking a patient off, but I don't know that we have a ready answer from the data that we have.

DR. SWENSON: I wonder if Dr. Pavord would comment on that.

DR. PAVORD: I haven't see any evidence that this drug changes the natural history of the disease, and the only data we have on withdrawal of

treatment suggests that they return gradually to their baseline status, so yes, a long-term treatment.

In adolescents, it may be a bit different. It's a very turbulent time. Any of you who have looked after adolescents will realize that there is a lot going on. But some do have genuine severe eosinophilic asthma, and it is absolutely catastrophic. They have a requirement for high-dose oral steroids, and these are terribly difficult drugs to take at that age.

So I can see a justification for a bridging period of treatment, and I think we're going way beyond the data. But these are a particularly difficult group of patients.

I recognize you've got a very difficult decision to make in this group of patients, but I would encourage you to consider the impact of this disease in this group of patients.

DR. SWENSON: I have a question on the issue of malignancy. I think that given the relatively small numbers of subjects studied, the relatively

short length of time, and data that suggests that eosinophils may be part of a broad-based immunosurveillance, and if you look at biopsies of tumors, you will see eosinophils in the picture, does the agency have any plans about this issue or, in general, what about malignancies as a risk factor in drugs of this nature, which perhaps might be used lifelong?

DR. CHOWDHURY: This is an interesting question and let me just take that in a broader perspective. Generally, when you have a biologic being evaluated for any disease, the risk of infections, opportunistic, and physical malignancy are a consideration. But those are considerations in the vetting of a broader immunosuppression by targeting something which is more innate maybe in the system. And the clinical trials data show some signals of opportunistic infections with or without malignancy.

So for this particular product, it is pretty targeted to a pathway which has not historically been linked to malignancy. IL5 has historically

not been linked to malignancy. And the amount of immunosuppression that is seen in the clinical program, while targeting IL5, is not generally as profound as we have seen in some other biologics targeting pathways such as IL1, IL6 or TNF, which is more in the immunity pathway.

So a priori looking at the molecular basis of action, looking at the data that we have seen in the clinical trials, malignancy does not come up something that is very concerning. If you as a committee think otherwise, we would like to hear that.

The question then, if you suspect or if you want to assess malignancy, how would you do that? So it is very difficult actually contrary to thinking. If you do not see any signal in the clinical trials database, how would you assess that, if you want to assess it postmarketing?

Another question is even why would you attempt to do that if you don't see a signal in the clinical trial database and the basic mechanism to suggest there is one?

So basically then, in the summary, we really have not been extremely concerned about malignancy. But if you think otherwise, we'd like to hear that.

DR. SWENSON: But the fact that you investigated it does speak to a possible concern. Does the agency have plans to include this in a long postmarketing sentinel event type monitoring or however this might be done?

DR. CHOWDHURY: Interesting that you bring it up. If there is a general feeling amongst the committee that it is something that we should think about, then we would like to certainly hear that and consider doing that.

The example that sort of comes into play related to this is that targeting antibody goes to IgE, which was approved by the agency a long time ago. And that actually in the clinical trials database had an imbalance of some tumors; not a very big imbalance, but there were some.

Again, the appearance of tumors in that database was biologically difficult to explain. It came up very early on treatment. But that led into

a study looking postmarketing for malignancy. And the study I believe has been published is an Xolair study, and that did not really pan out showing a profound malignancy signal.

So having gone through that experience, I think, setting something up for this particular molecule without having a prior risk that comes up with the clinical trials, is something which I think we have to think about if you think it is reasonable for us to consider.

DR. SWENSON: Dr. Georas?

DR. GEORAS: I'm glad you brought that up because I was going to bring this concern, as well. I personally wouldn't say it is an extreme concern, but if we're thinking about potentially lifelong therapy, I think there is enough epidemiologic data, as well as preclinical data, suggesting that eosinophils under some circumstances can contribute to anti-tumor immunity. But I think it should be on our radar screen.

I will acknowledge the epidemiology is muddy with some studies showing a positive prognostic

value of tumor eosinophilia, but others showing the opposite, as is the preclinical data, with some studies showing that eosinophils contribute to anti-tumor immunity, but others showing that eosinophils play a role in tumor progression.

So I think the field is muddy, and I wouldn't put my level of concern at extreme. But in my own opinion, as we're moving into human immunology manipulation, I think it should be something to be monitored.

DR. CHOWDHURY: I totally agree, and we will take that advice under consideration as we move forward. I think the confounding issue in this is this is very difficult to tease out, really if you think about it, in a postmarketing situation or others, given the experience that I just shared with you very briefly about the anti-IgE molecule.

Also take into consideration that if you think about why malignancies should appear with this molecule, it really is suppression, general sense, of the immune system causing the malignancy to come up. That's really the mechanism for

biologics targeting the immune system; or as you brought up, which we have investigated over eight years, Th2 IgE molecules having some [indiscernible] functions.

The problem is these patients are going to be on probably a pretty high dose of steroids, oral and also inhaled, and that also has immunosuppressive effects. So teasing out from this patient population some other immunosuppressive drugs, possibly a steroid, is going to be rather quite challenging. And also to think about it, what would you do with that information if there is very small number of imbalance, which is not necessarily very compelling? Because these patients are also quite sick.

So it's very difficult for us to conceive any way of looking at it postmarketing. If you have any suggestions, we'd like to hear that.

DR. SWENSON: Well, there being no questions, if I'm correct, if no one has any questions to the agency, we will resume again at

1:10. Enjoy lunchtime.

Just as a reminder to everyone on the panel, no discussion of the issues at hand at lunch.

(Whereupon, at 12:02 p.m., a luncheon recess was taken.)

A F T E R N O O N S E S S I O N

(1:09 p.m.)

DR. SWENSON: Welcome back, everyone. We will resume our discussions.

At this point in the meeting, we would often have an open public forum, but we've had no requests for any public testimony. So we will proceed on with the last half of this meeting.

But before going into the charge to the committee and then discussion of the different issues around safety and efficacy, there was a question raised to the sponsor from Dr. Morrato, and the sponsor has a table they'd like to show us.

MR. YANCEY: So if we could have the slide up, please. This was in response to the request you made. I think we've tried to make this as simple as possible. Let me walk through it and try to take any questions you may have afterwards.

This is simply looking at the opportunity for patients based on the eosinophil thresholds. This is an analysis of the combined data from study 997 and study 5588. If we start on the

left-hand side of this particular table, we've listed meets both criteria; if we look adjacent to that box, meaning simply that they had the positive baseline value of greater than 150, as well as historical greater than 300. Baseline only would be they have the 150 value without a record of greater than 300 historical, and I think you can follow that on through.

So if we look at what would be the third column, listed is the number of patients that contribute to each of those cells, as well as the percent of patients contributing from the total. So we can see that 61 percent of patients met both criteria, resulting in a 52 percent reduction. And you can see the rate ratio and the corresponding confidence intervals in the column beside the percent reduction.

Baseline only, no historical of greater than 300, that's 19 percent of the population, representing a 56 percent reduction in the rate of exacerbations compared with placebo.

Historical only, this was the one you were

specifically about, this would be yes to the historical, but no to the baseline. In the combined data set, that's a 33 percent reduction in exacerbations, and having the neither represents the 10 percent reduction.

Maybe there is some additional value if Dr. Pavord would just speak to the relevance of the clinicians to have these options available to them.

DR. PAVORD: Yes. Thank you. The way that clinicians use biomarkers is that it alters the probability of a certain outcome, and the skilled clinician will know very well to what extent it alters that. And we'll always attach more significance to a clearly abnormal result or a repeatedly abnormal result than one off measurement.

Quite often in medicine, one seeks to get more evidence, so one would not make a treatment decision. You would keep testing and monitoring that patient. It is very analogous to the situation when you're having your blood pressure assessed. If you have a borderline result, you

would seek more evidence. You would think a little bit harder, whereas if it's clearly abnormal, you might take more decisive action.

Now, in the UK, patients referred to my severe asthma clinic have, on average, seven full blood counts available in their electronic record. So there's a lot of that information already available to you. And if all seven are clearly abnormal, the patient is exacerbating, I don't really need anymore information. And similarly, if they're all normal and the patient is exacerbating, I would think this is a different inflammatory pattern and likely to respond to treatment.

So I think that this reassures me that both criteria are valid. Clearly, the more abnormal the blood eosinophil count, the higher the likelihood of a treatment response, and the clinician will know that.

DR. SWENSON: Thank you very much. We will now move into Dr. Gilbert-McClain's charge to the committee, and a discussion, and focus on the questions at hand.

Charge to the Committee - Lydia Gilbert-McClain

DR. GILBERT-McCLAIN: Thank you, Dr. Swenson.

Good afternoon again. Over the next few minutes, I will review the questions that you have been asked to consider and provide some clarification. But before we review the questions, I wanted to remind you of some of the regulations regarding FDA's standards for approval and non-approval of an application.

So the regulation says that the FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling. And as I mentioned in my remarks this morning, that the focus of today's meeting is to discuss efficacy and safety, and manufacturing, controls, and labeling are not part of the discussion for today's meeting.

The efficacy standards are shown on this slide, and it basically says that there is a need for substantial evidence consisting of adequate and

well controlled investigations, that the drug will have the purported effect under the conditions of use recommended in the proposed labeling.

In terms of safety, the CFR standards for refusal to approve an application for safety essentially encompasses four points: one, that the application does not have adequate tests or studies to assess safety; or, that the studies show that a product is unsafe; or, studies do not show that a product is safe; or, there is not enough information to determine whether the product is safe under the proposed conditions for use.

So we would ask that you keep this framework in mind as you discuss the questions in your deliberations today.

So as I said this morning, there are a total of five questions. The voting questions are broken out into adult and pediatric questions. So in reality, you will be voting -- you will be casting six votes, because the voting questions, you have to vote for the adult population and the pediatric population. And there are two discussion

questions, one for efficacy and one regarding safety.

So let me walk you through the discussion questions. For the first question, we are asking you discuss the efficacy for mepolizumab administered once every 4 weeks to support its use in the treatment of severe asthma.

Again, as I mentioned this morning, if you notice in the discussion question, we are not specifically reiterating the proposed indication statement that was framed by the sponsor here today, but we want you to consider specific issues that would help us and guide us as we think about how to arrive at an indication statement.

So we would like to hear discussions on the asthma severity of the patient population. We would like to hear your feedback. We heard some clarifying questions this morning about eosinophils, about the stability, about the historical numbers, and generalizability, et cetera.

We want to get your feedback on the role of

eosinophils in determining initiation of treatment with mepolizumab, and then we want to hear from you as you discuss the efficacy in the pediatric population what you think about those data.

We heard this morning that the patient population, the numbers were actually very small, but we also heard that there could be a need for this product in the younger population.

Finally, in your discussion, we want you to deliberate on the ethnicity of the study population as a reminder that the African-American population, the numbers are very limited.

Next, we would ask you to vote on the efficacy, and the voting question asks you, do the efficacy data provide substantial evidence of a clinically meaningful benefit of mepolizumab 100 milligrams subQ once every 4 weeks for the treatment of severe asthma?

As I mentioned, that question is broken out into two parts, in adults and children. So you will be voting on each of those populations separately. And if not, what further data should

be obtained?

Next, we would like a discussion on the safety data that was presented to you today. Again, we would like in your discussion that you talk about the size of the overall database and the adequacy of the safety data in the pediatric population.

Then question 4, which would be a voting question on safety, has the safety of mepolizumab 100 milligrams subQ administered once every 4 weeks been adequately demonstrated for the treatment of patients with severe asthma? And, again, in adults 18 years of age and older and children 12 to 17 years of age, you will be voting on each of those populations separately. And if your answer is no, what further data should be obtained?

Again, as a reminder, we always like when you vote, that when you respond, whether you respond yes or no, that you provide some context as to why you voted the way that you did, which also helps us in our deliberations.

The final question, which will be a voting

question, is the approval question, which would take into account your voting on the efficacy and the safety. Do the available data on the efficacy and safety support approval of mepolizumab 100 milligrams subQ administered once every 4 weeks for the treatment of patients with severe asthma? And again, broken out into adults and the children. And if not, what further data should be obtained?

So we look forward to the discussion this afternoon, and I turn the podium back to Dr. Swenson. Thank you.

Questions to the Committee and Discussion

DR. SWENSON: We will now proceed with the questions to the committee, as you have heard, and then discuss as broadly and deeply as you wish.

I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

So we are focusing now on question number 1 around the issues of efficacy for the drug and particularly the subgroups that were just

discussed.

I would like to open up for questions. And particularly those that haven't on the panel asked any questions, please, we also need to hear from you, if you feel that you have something that we should be discussing.

We'll start off with Dr. Stone.

DR. STONE: Could I just ask -- so when the FDA presented, they showed the distribution of eosinophil counts from two of the studies, but not from study 75. Do you have that data? That's the population I imagine is enriched in patients on oral corticosteroids.

DR. ABUGOV: I do not have that data.

DR. SWENSON: Okay. Dr. Blake?

DR. BLAKE: So my question is for the sponsor. Since these were patients who were supposed to be on high-dose inhaled steroids plus an additional controller medication, what data do you have on how adherent they were with their controller medication? Because we know in trials where the ICS plus LABA is prescribed as part of

the study, then adherence is very good. But if it is just background treatment, adherence often is not very good.

So I'm just wondering that if these people are not necessarily adherent and we have a nice effect, what is going to happen in patients who are really well adherent with their ICS and LABA, are we not going to see maybe as big of an effect? Given this is probably going to be an expensive drug, I think that's something that would be of interest.

DR. ORTEGA: The question you are asking is quite relevant in this particular population who are patients with severe asthma and with the requirement of optimized therapy.

So in our program, what we did was ensure that that information is captured in the chart. As you know, adherence is always a challenge to confirm the actual utilization of the medication. But at least in our program, once again, we ensured that there was documentation in the chart utilizing our monitors to ensure that that information was

captured.

I think there are two elements that also give us further reassurance that these patients were adherent to their medications. One was in the study 575, for example, the steroid-sparing trial. When the steroids were reduced during the trial in the placebo group, it was very evident that the levels of eosinophils started to increase somehow, which suggested that these patients actually were adherent to their medication.

Another sort of evidence that we have to suggest that these patients also were adherent is at the completion of the trial, 95 percent of these patients opted to enroll in an open-label extension study, considering there were no other options out there for these patients to continue maintaining their control.

DR. SWENSON: I have a question that relates to the obviously small numbers of subjects of African-American descent. And the issue, in my mind, is that the point estimate appears to be equally good for exacerbation rate reduction, but

the confidence intervals are so broad that they cross 1.

But at the risk of being very strict in terms of saying, well, then this group simply has no statistical evidence for efficacy, might we deny a real benefit to a small group of patients?

I wonder -- if amongst the statisticians and other people that are far more versed in this than myself as to whether if a point estimate on an effect is as good as the point estimate on other subgroups in which the confidence intervals are very narrow -- can we assume that that simply is just a problem of small numbers that would happen no matter what you were looking at? And should we be assuming that that point estimate for African-Americans is likely a good one and we ought to consider not putting any further strictures on the use of the medication to certain groups?

I am opening that up for just any discussion. I see John Connett would like to comment.

DR. CONNETT: You can assume it, but you

don't have much confidence in that conclusion. Wide confidence intervals, they are what they are. They could be quite different. I think that is the situation that we have.

DR. SWENSON: Dr. Follmann?

DR. FOLLMANN: Yes. I'd like to add something to this, as well. What John said is right. If you just look at the subgroup in isolation, it has a wide confidence interval, but we didn't really do a study in African-Americans alone and have a wide confidence interval. The study was done on the entire population.

So to me, the natural way to approach subgroups like this is to look for evidence that they are different. So a statistical way to do that is to do a test. Is the rate ratio the same for African-Americans versus not?

The FDA didn't really report on that, but by eye it is quite clear that such a test of interaction -- is there a differential effect between African-Americans and non-African-Americans -- would show that there is no evidence

whatsoever.

So if that is the case, unless there is some mechanistic kind of reason or other evidence or other arguments other than just, gee, it's a small sample size, my inclination is to -- from clinical trials 101, we randomized this population, let's make the generalization to this population, as well.

You can continue this thinking, and maybe there's like a genetic cause of asthma that we might have measured in this study, and then we could look at whether or not the effect is similar in this group that has the mutation. You could look at people who have baseline eosinophils of 150 to 160.

Again, you'll have these small, small subgroups. By construction, the sample size will be such that the confidence interval will include 1. And so you can nibble away and nibble away at the population until nothing is left.

So given that this is how the study was conducted and we don't have any evidence that it's

different, my inclination is to accept it and generalize the results of the entire population.

DR. SWENSON: I'm going to just take us out of line here, Dr. Morrato, and let Dr. Au -- I think he has a point to raise, and then we'll come to you.

DR. AU: This is just a follow-up. On slide number 39 from the FDA's presentation, the point estimate for African descent is actually higher than from study number 97. And so there actually is potentially some differences based on -- at least based on limited evidence. Granted, the confidence intervals are huge, right?

But this does suggest that there might be something different. All we know is -- all we think is that the true point estimate or the true effect is somewhere in that confidence bound.

DR. SWENSON: Dr. Morrato?

DR. MORRATO: I was wondering, to your question earlier, whether or not the sponsor has data on the eosinophil distribution that you were asking. I know the FDA doesn't. Was that

study 75? The distribution of the baseline, I think that's what you were asking.

MR. YANCEY: Apologies. The audio is a little bit challenging on your question, so I'm going to repeat it and make sure we have it correct. I think you're just asking for what did the baseline eosinophil distribution or baseline geometric mean look like in African-Americans and adolescents compared --

DR. MORRATO: No.

MR. YANCEY: No?

DR. MORRATO: No. I was getting back to the question -- I can't see the name tag -- the question from Dr. Stone. He was asking to see if there was -- repeat your question. I can't.

(Laughter.)

DR. STONE: It was just the eosinophil distribution was shown for studies 88 and 97, but not 75, where there is probably a greater number of patients on oral corticosteroids. And I think you used the same enrollment criteria of greater than 150 or historical of greater than 300.

MR. YANCEY: Thank you. So the FDA presentation was done in a different manner than we as the sponsor had presented. So maybe I can provide you some reassurance that actually they are actually quite similar by just speaking to the overall geometric means.

So if we think back to the exacerbation studies, those geometric means were ranging between 240 and 290 cells at baseline. If we look at the OCS-sparing study, they are quite similar and that their lower range is 230, and I believe the upper was 270. But I would need to check that number.

But nonetheless, they are quite similar, which would suggest to me, without seeing the distributions, that even the distributions would be similar, but I don't have that information.

DR. SWENSON: And just along those lines, did you see the same fall in eosinophils in that subgroup like we have seen the data for the group as a whole?

MR. YANCEY: So along those same lines, in both studies, the mean reduction was about 80 to

85 percent from baseline. That translates to a geometric mean of about 50 cells per microliter. And what we see in both the exacerbation studies, as well as the OCS-sparing study, is that drop to around 50 to 60 cells per microliter.

So the overall performance in both of those populations is incredibly similar.

DR. MORRATO: I wanted to comment on the question around the wide -- another point to consider when thinking about the efficacy in the small group analysis, in my mind, could also be the biological basis for why we might suspect we would see something different in African-Americans or children.

I didn't see any evidence of that necessarily among African-Americans, but there were a couple of points mentioned in the briefing documents that the mean age of the population was 49; the fact that there are comments that IL5-related severe asthma develops in older adults; the eosinophilic-driven phenotype is more common older adults.

Now, it may occur in children, but I find evidence in 26 children not very compelling to support efficacy there. And it seems like the biological orientation of this kind of disease, not to exclude that there are young people who are affected, is predominantly adult.

So that's how I was reading what was -- or interpreting what I was reading.

Can I add one more thing?

DR. SWENSON: Yes.

DR. MORRATO: To the earlier question around did you see good drug adherence in the placebo arm and how that might affect the translation, I think it's worth noting that there was an expert editorial commentary when these data were published in *New England Journal*, and they actually made the point of the astounding placebo effect in the trials and whether or not, gee, if we could only get great treatment on the regular stuff, do you need extra.

I think it's good just to mention that this is a monthly administered drug in which the patient

has to come in, and there is probably beneficial therapeutic effect of having that aspect, as well.

So what you may have seen in the placebo is the impact of not just them complying, but they're seeing their provider once a month.

DR. SWENSON: Dr. Davi?

DR. DAVI: I have just a couple of -- two clarifying comments I want to add to the discussions that are ongoing. First, our not showing the baseline distribution for the eosinophil count for the corticosteroid study, we did not intend for that to imply that we thought that study was different in some way.

So I just wanted to clarify that point because perhaps that was a misimpression. In fact, data that we did show indicates what the sponsor indicated, which is that the geometric mean and the range was quite similar in terms of baseline eosinophil count. We just don't have the histogram that you asked for.

Then the second point I wanted to make on the question about examining the treatment by race

interaction that Dr. Follmann suggested, we did do those tests. With the limited data that we have, there is no suggestion of a differing treatment effect across race, but it's limited by the size of the small samples.

DR. SWENSON: Dr. Dykewicz?

DR. DYKEWICZ: Just one comment in follow-up to Dr. Morrato's point. In terms of the placebo group improving from baseline, besides the adherence factor, there also is the natural history of asthma factor.

We know that asthma is not a static disease and that it can improve and worsen with time. I actually remember being a fellow way back in the 1980s where I had an assignment to write a paper on the natural history of corticosteroid-dependent asthma, and at that point we were just talking about inhaled steroids, but at least good third of people over a year or two would get significantly better. So that is one of the factors that could be at play.

DR. SWENSON: Dr. Raghu?

DR. RAGHU: Thanks. We're dealing with a single study for dose reduction of corticosteroids. I'm a little bit concerned about the reduction of the daily prednisone based on one single study.

My question relates to the earlier question that I had asked. In the open-label extension study, there was a decreased reduction, which is what the sponsor said very clearly. But is that true for the corticosteroid reduction dose, as well, in the people who received the open-label study after the 24-week study, specifically the 61 study, which is the 52-week study and conclusion study?

So in other words, was the dosing of the corticosteroids reduced seen in the people in the 52-week study, as well?

MR. YANCEY: So you may recall from the presentation from Dr. Ortega that at the end of the randomized control trial that the median reduction in patients receiving mepolizumab had moved to about 3.1 milligrams. It remains in that same range once they go back onto -- no, I'm sorry.

These are patients who were on mepo, and then they continue in the open-label extension.

So there wasn't an increase or a decrease. They're staying the same. I don't think we have a backup slide on that to show, as these data have just been reported to us. In other words, there is no worsening. They are maintaining their reduction of steroids.

DR. RAGHU: What about the placebo arm, people who got the drug in the open-label extension, did their dose get reduced with the prednisone?

MR. YANCEY: I'm going to have to ask Dr. Ortega to answer that question.

DR. ORTEGA: In the 661 trial, in contrast to the randomized trial, we allowed physicians to reduce steroids without any specific guidance, but according to standard of care.

Patients who were on placebo were able to reduce 50 percent their dose from the dose that was at the end of the randomized clinical trial, which translates into about 7 milligrams of prednisone.

DR. RAGHU: Has the FDA seen this data? I just wonder because there is a paucity of the data on the open-label extension, that while there is a clear concept, there is no question. But to me, in terms of what exactly was captured in the open-label extension in terms of the dosage for the people who were in the placebo post-open label is what I am looking for.

MR. YANCEY: Those data are not shared with the agency at this point in time. The clinical study report is being drafted. But we will share this with the agency probably within the next 4 weeks.

DR. SWENSON: Dr. Follmann?

DR. FOLLMANN: One of the comments or one of the things we're supposed to comment on is the role of eosinophils in determining inclusion criteria, I guess. And I thought the sponsor's slide A-51 was pretty compelling to me in terms of realizing this was a good marker.

We see strong effect modification by that and, importantly to me, at the point of the 150

cells at baseline, we had substantial and statistically significant benefit for both studies at that point. So I thought there was a strong case made that this is a reasonable cut point and a strong case made that it tracked with severity, as well.

DR. SWENSON: Dr. Georas?

DR. GEORAS: I would agree. I think the efficacy data is compelling, and we're struggling with trying to characterize a very heterogeneous disease and to find the appropriate phenotype.

But getting back to that slide or maybe the table that you presented after the break -- and thank you for that -- I'm still trying to understand what the historical value of greater than 300 brings to the indication.

I understand it's about 13 percent of the cohorts in your studies, but the reduction in exacerbation was lower with confidence intervals that overlap 1.

Maybe I can phrase it as a question to the FDA. Do we have a sense of what a clinically

meaningful reduction exacerbation rate is? Is 30 percent something that has been considered significant? If somebody is exacerbating three times a year and you go to two, is that sufficient?

DR. CHOWDHURY: Maybe I can take this question. To answer your question directly, no, we do not have a number that we rely on for clinical significance of exacerbation.

Having said that, exacerbation is a very significant event. So we rely on statistical significance. And if you see a difference which is true and not even by chance, we accept that. So that is the direct answer to your question.

You brought up, and I want to bring back to the commenter here, between the eosinophil count at baseline versus the eosinophil count historical, and this is something I think we will benefit if we can discuss that further and give us some input.

I want to also remind you and bring that question that I am raising here back to the indication or the target population. I think the target population is a better word to use.

If you think for the target population the clauses are N, so patients are exacerbating despite being on maximum controlled therapy, at that time the eosinophil count is high. Historically, there was a term used, "refractory asthma," meaning patients are taking steroids and they're not still responding.

So this is the target population that we showed. The eosinophil count is in the context of the person exacerbating plus they are taking maximum treatment.

The question that we want you to discuss and give us some input, in the historical eosinophil increase, do we know it is still the case the patients were having exacerbations and they were actually taking high-dose steroids, inhaled plus oral, at the time the eosinophil count was still high?

For the immediate baseline that can be easily ascertained, historically, we are not sure, and we want to get you thinking about that and give us some input. Thank you.

MR. GEORAS: Maybe I can phrase that to the sponsor. In that 13 percent of subjects where there is historical only -- in other words, the historical count was greater than 300, but the baseline was less than 150 -- were there other outcome measures that were positive, such as quality of life or other indices that you have in that subset?

MR. YANCEY: So given that that is such a small group, that 13 percent, that provides a 33 percent reduction in the exacerbation rate. Because it's a small rate, we didn't continue to slice and dice those data in looking at SGRQ or ACQ. So I'm unable to provide you additional information.

DR. ABUGOV: I think it's worthwhile to point out that the sponsor's reduction of 35 percent among those patients was gained by merging the two trials.

In study 97, all of the patients had some type of -- some other indications of the eosinophilic asthma, such as nitric oxide above 50

parts per billion, higher sputum eosinophil counts. And merging that data with that from study 88, in which the only indication of eosinophilic asthma was via eosinophil count, I don't think that's productive.

Again, if you bring up study 34 -- I mean, slide 34 -- what you can see is that those patients below 150 eosinophils per microliter, those patients were enrolled solely because of a history of eosinophils greater than 300 in the past year.

We are not seeing much of an effect there, certainly not in the range of a 30 percent reduction or 35 percent reduction in eosinophil -- in exacerbations.

DR. SWENSON: Let me ask a follow-on on that.

DR. ABUGOV: Sure.

DR. SWENSON: If, as you say, a single 300 at some point in the past year does not offer any guidance, it seems a bit striking that 150 at the time of possible initiation then would be an indication to proceed. Do you see the slight

conundrum?

DR. ABUGOV: I do, and there have been studies regarding variability of the eosinophils. First, the criterion 300 eosinophils in the past year, what does that mean? How many times were the patients measured? If somebody is measured and gets an eosinophil count 10 times in the past year, of course they are more likely to have at least one count greater than 300.

Also, in this study, within this study, all of the eosinophil counts were on one type of counter, the Coulter LH 750. I didn't see any indication in the sponsor's submission that other types of counters weren't used, and there is a huge variability between counters.

So those earlier readings of 300 might mean a lot on one counter, but they might not mean a lot on another counter. The reference ranges vary between 4 and 800 eosinophils per microliter for the different counters.

DR. SWENSON: Dr. Davi?

DR. DAVI: I just want to reinforce one

fundamental point that Dr. Abugov made, which is that the 33 percent ratio that the sponsor is showing you for patients who were enrolled only based on historical criteria is probably affected by the fact that although they were enrolled based on that historical criteria, the study was enriched for patients who have other indicators of eosinophilic inflammation.

So that group of patients probably has eosinophilic inflammation, and so the efficacy probably looks somewhat better there than it did in study 88 where the criteria for enrollment was simply based on the historical measurement of eosinophils or the baseline measurement of eosinophils.

So it's the fact that study 97 had those additional eosinophilic enrichment criteria that could be making the efficacy look better for that group.

DR. SWENSON: Dr. Morrato?

DR. MORRATO: I just wanted to comment on that. It may be more along your line -- the

evidence of eosinophilic elevation, which could be measured and is a baseline reading of X or that that's really the concept of trying to get across maybe as you work through the indication as opposed to slicing and dicing.

I do take to heart what Dr. Pavord was saying in that if you do have good historical documentation in your electronic health records of repeat measures and you can justify there is evidence of it, does it mean you have to retest at that moment and order another test?

I don't know if FDA has a point of view on that or not. Or is it really just the fact that they have established disease that's related to elevated eosinophils?

DR. CHOWDHURY: This is sort of the conceptual thing that we want to get you to discussing, that you are doing, which is really helping us, and we don't necessarily have any a priori idea coming into it. I think conceptually it seems very reasonable what we are discussing here, that patients with an eosinophil kind of

phenotype would probably benefit with this drug.

As you have heard from Dr. McClain and others earlier on, we want to make sure patients who would get benefit would get the drug. At the same time, I think everybody's aim is not to give the drug to somebody who may not actually benefit.

So this is a very fine boundary to, I think, walk through. And I don't think we should think too much what the indication language is going to be. And based on the discussion, there may be some reasons not to even measure the eosinophil count of indication and leave it to clinicians' judgment, because if you do a count, then everybody will go by that count, and it may be something that one might not necessarily micromanage.

But leaving the indication language out, just conceptually, if you think about it, we look at these studies 88 and 97 and conceptually accept there is an eosinophil-exacerbation effect interaction, which is positive. We'll accept that. If we accept that, and then you look at this, well, those with historical eosinophils of 300-plus, the

effect is more like zero. You almost have to also accept that.

So that is the dilemma that we are having. If we accept that, then what does the historical eosinophil count mean? And if you really enroll patients based on that, are you enrolling patients who might not benefit? So going too much into numbers has that risk of opening up in both ways.

So I think what you are discussing is helping us and we would appreciate if you have any recommendations for us. Looking at this, I think we are getting a sense that the eosinophil before the drug is given is quite reasonable as far as interaction goes. The historical one, I think there is some struggle what to make of this. Thank you.

DR. SWENSON: Dr. Connett?

DR. CONNETT: A couple of questions. One is related to this discussion I think. If you look at FDA's slide 32, it shows the screening blood eosinophil counts, and it's clear there that -- first of all, there are a few that are down

very close to zero, but really the mean value is probably up in the range of 400 to 600. The fact that it's at least 150 at baseline does not mean that it's 150. It actually tends to be somewhat higher than that. So I think that's a factor in this, as well.

The other thing I wanted to comment on was the company's slide A-7, which is the proposed indication and dosing. On their indication and dosing, they discuss the eosinophil counts, but the final statement that they have in that box says, "Nucala has been shown to reduce exacerbations of asthma in patients with an exacerbation history."

I think if that last statement is taken out of context, somebody quotes it, they will end up treating patient where it is maybe not justified because they don't have elevated eosinophil counts.

So I would think maybe that last statement ought to be qualified, just as the rest of the paragraph is qualified.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: Thank you. This is actually

a follow-up question to study number 75. I'm going back to the question regarding children ages 12 to 17. The study where the corticosteroid dose decreased did not involve children -- I think that the youngest age was 18; is that correct? I'm wondering if the sponsor has plans to then study that population so that we can answer that question.

DR. ORTEGA: That study also included patients 12 years and older. There were only 2 patients enrolled in the age group 12 to 17. That was your question?

DR. CARVALHO: And the second part was, is the sponsor planning to study this population a little bit in more depth?

DR. ORTEGA: We continue to -- we have other ongoing studies where we continue to study patients with asthma ages 12 and older.

DR. SWENSON: Dr. Follmann?

DR. FOLLMANN: I wanted to just make a few comments about the utility of the historical eosinophil count greater than 300. We had talked

about that earlier, and the 13 percent and should they be included in the dosing or the recommendation labeling or not.

I understand and appreciate that the historical eosinophil count can be kind of messier than the other one. It might be based on different measuring devices. It might be based on many measurements or few. But nonetheless, it was sort of what was used in the trial for inclusion criteria.

I would recommend that you do a test of interaction like I talked about before to see if that 67 -- or is it 33 percent reduction rather? It really does statistically differ from the other groups. I suspect it won't.

I understand that we feel a little uncomfortable combining studies sometimes, but I think when we're looking at subgroups, we're hampered by small numbers, and so we should combine. We can maybe stratify by study or include study as a factor in that to adjust for that. But I still think lumping those studies to get a signal

on these smaller subgroups is important.

Then finally, if the test of interaction doesn't come out as showing that it's really different there, where is the evidence to deny this group this drug?

DR. SWENSON: My question gets to the issue of what would be a meaningful rate of exacerbation reduction. To my mind, I think globally this 50 percent from something over 2 to something just a little over 1 is meaningful, but perhaps there are some people on the panel that have a better grasp of patient-centered outcome and translation into quality of life as to is that a meaningful number.

I think that gets to the question of perhaps the agency wanting to include some measure of severity of exacerbation frequency as part of the labeling.

(No response.)

DR. SWENSON: We'll leave it at that then. Dr. Raghu?

DR. RAGHU: Going back to this historical

300, I still don't have a feeling of chronology of when that historical eosinophilia was. Does anybody have a feeling? Is it within the last 6 months, or within the last 12 months, or when?

The other question related to it is how many of those historical eosinophil people had also the baseline screening of 150?

DR. CHAUDHRY: Sofia Chaudhry, FDA. I believe GSK has a slide showing how many patients met the 300 and the 150; is that correct?

DR. RAGHU: Both historical presence of 300, as well as the screening of 150.

DR. CHAUDHRY: I believe they have that data. My understanding is the 300 count had to be within the previous year.

DR. RAGHU: So 13 percent of the people who had the historical group, how many of those 13 percent had the base line is my question. I know it is either/or because you are lumped in for a baseline screening of 150, or they could have had a 300 at any time 11-and-a-half months before.

So my concern is that technically a person

could have been in the study with one 300 cell count 11 months and 3 weeks before entering into the study, with the baseline screening of normal eosinophil count and without other categories.

MR. YANCEY: I understand your question. I'm not going to be able to give you precise data or a response with regard to the exact timing of the historical counts or the number of historical counts.

Dr. Pavord has given us information. These are patients with very severe asthma. They also have a lot of comorbidities. So they are frequently utilizing the health network. So common blood CBC is actually relatively common, and I think that was illustrated by his comment.

The limitation of the database, the sponsor database, is we collected those data by a question of do you have a history -- is there a documented history above 300. In hindsight, perhaps we could have asked that question differently and captured the information around are there multiple records that were performed and what was the timing of

those records, but that's a current limitation.

But I think what you're driving toward is trying to understand exactly the utility of the historical value. And Dr. Pavord has provided, I think, some excellent evidence saying that in the hands of a skilled clinician, he would probably not consider someone perhaps with a single record of 300, but he had a patient with many records with a very robust history of exacerbations. That would be a clear candidate, in his view.

There is also the patient-centric approach to this. A lot of these patients with severe asthma are making frequent visits to the health care system, and if there is that ability to use clinical judgment based on the available information, it would also suggest that there would be a good response in most of these patients.

The likelihood is that it would be something that would be available to that patient if they were, at the time of the clinic, available to take care and not have another requirement for an additional test. There is also just a patient-

centric element to that. I know I can think of examples of where that actually would become very important.

DR. SWENSON: Dr. Evans?

DR. EVANS: I think we've seen good evidence that increasing values at the baseline using eosinophil counts are associated with better treatment response.

This is a question really to the agency. That is, is there a reason to think that we should use a higher cutoff than 150, although the sponsor's model says 150? And the reason I ask is it seems that there are other agents that are being tested in the IL5 axis here for a similar population, and recent trials there seem to have required for reslizumab 400 or greater at baseline and for benralizumab for greater than 300 at baseline.

So is there data that the agency has that points to a higher number being better outside of what we have seen today?

DR. SWENSON: Dr. Davi?

DR. DAVI: I don't think we have a position today that we want to endorse a different number, but I just want to provide a little bit of information that might maybe aid the discussion.

You might know that the FDA has a biomarker qualification program where biomarkers are evaluated outside of the development of a single therapeutic product, and in that setting, we have a couple of cases where we are evaluating predictive biomarkers using continuous values for the biomarker.

We do not impose a cutoff for the calculations, and we do not ultimately recommend a cutoff. And so that is one possibility, that you could describe the relationship between the treatment effect and the biomarker and leave the choice about whether or not the product would be helpful to the hands of the user.

DR. CHOWDHURY: I just want also to bring in some context to the discussion here. You are raising an important point about some other products having some publication with some

different numbers.

We are aware of that, but I don't think we are in a position to discuss all the drugs together and come up with a magic number. If you could, that would be very useful. I think for the time being, we are discussing about the specific product.

At some point, my understanding, when many of these drugs or drug classes come to the market, the academic community can get together and put their heads together and come up with some numbers.

So at this stage, what you are referring to is other products and external numbers. I think it is not something that can be done or is going to be very useful.

Also, keep in mind some of the products may not necessarily been targeting just IL5. Some of the products that you mentioned actually may be targeting something else in the same Th2 pathway, not exactly IL5.

Also keep in mind that the anti-IgE molecule that was discussed a long time ago targeting IgE,

there were some abstracts presented at meetings showing they actually have a beneficial effect on sort of eosinophilic kind of phenotype.

So that really draws in a lot of issues for consideration. So what we are thinking here is looking at the data, what is the number that you think is reasonable and not really try to make a cutoff.

Also, keep in mind this particular product was studied in a very targeted population. Eosinophilia is one of the criteria. To get to there, the patients have to have asthma uncontrolled despite being on everything else.

Some others that you mentioned, if you go back and look at them deeply, you will see that that was not the case. So if you have patients who are lesser sick, if you would call it, then if you catch this patient with high eosinophil count, that's different than this very sick patient with a different eosinophil count.

So there are multiple things in play here. So that's the reason we are trying this specific to

this population, which is very targeted.

DR. EVANS: I do understand that. I'm just trying to take advantage of -- since this is the first agent of its kind to hit the market, or potentially, I'm just suggesting that we take advantage of all available information.

DR. CHOWDHURY: I do much appreciate it. And if you have any thoughts to share with us on this, please do. We will absolutely take this into our consideration and thinking process. Really appreciate your thought on this.

DR. SWENSON: Dr. Blake?

DR. BLAKE: So this is probably a question for the sponsor, and it has to do with the African-American population.

In the FDA slides, they separated out study 997 from 588 and the confidence interval was wide for study 88 and less wide for study 97, and then when you combined them, the confidence intervals looked similar to study 97, which had more African-Americans.

So my question is, how many

African-Americans in study 97 met the entry criteria for one of the two eosinophil entry criteria versus one of the other -- exhaled nitric oxide or one of the other ones?

So I'm wondering if there is something else about African-Americans rather than eosinophils that is important compared to whites, for instance.

MR. YANCEY: I completely appreciate and understand your question, but you're going to be disappointed in my answer. So again, you're going to be into very small subgroups, 39 subjects total. We didn't take a position of being able to continue to divide these into similar points, and I think that principal was made by the statistician at the table.

We haven't done that. So that's the disappointing answer, we don't have that information.

DR. SWENSON: Dr. Au?

DR. AU: I was just wondering, in follow-up to that. These are patients of African descent and not necessarily just all African-Americans. Am I

correct in that? And then the second is, was there an attempt to kind of enrich the population for any particular subgroups, such as African-Americans, and does this represent just an issue of the biology in the population or is this something dealing with the study design and sampling?

MR. YANCEY: So in terms of African descent or African-American, just to understand how these trials are conducted, it's a self-report race or ethnicity report. So the vast majority of these patients are from the United States. So they are self-reported as African-American. There is very limited African descent data that's included in that.

There was a second element to your question and if you would repeat it, I'll try to address that.

DR. AU: Sure. I was wondering whether or not there was an attempt to enrich the population with any particular ethnicity, race, and whether or not this represents just kind of the phenotype of eosinophilic asthma, where it doesn't affect the

African population as much, or is this an issue of study design that could be addressed in another study or something else?

MR. YANCEY: So there wasn't an enrichment opportunity with regard to try to identify specific subgroups. We did -- and as Dr. Ortega reported, and I'm going to transition now to talk a little bit about adolescents because it's another subgroup that doesn't have high representation.

We were actually very disappointed to see the low numbers of adolescents, and he has reported that there was one. This type of trial, and it's the type of trial that we have run in mild to moderate asthma over decades of study, we would have seen much larger proportions of adolescent patients.

So there was an effort by the study teams, particularly in the follow-on studies 88 and 75, to ensure that we had sites who would make a verbal commitment to understanding our need to include both African-Americans and adolescents.

Having said that, the numbers went up

dramatically in 5588, but it was not translated into 575. I think some of that has to do with the fact that, at least in adolescents, and I've already made this point earlier this morning, the prevalence of this particular phenotype in adolescents is quite small, particularly relative to adults.

It doesn't diminish the need for this group. They are still experiencing two or more exacerbations. They are on high-dose inhaled corticosteroids. About a third of our population are receiving daily prednisone. So there is a high patient need here despite the fact that it's a very low prevalence group.

I think we also we've tried to present data that talks about the overall safety profile of the medicine, and it has been relatively similar to patients receiving placebo, and that was even at a dose that is tenfold higher than the dose that we are suggesting to bring forward.

So no enrichment opportunities. We did try to increase around both African-Americans and

pediatrics. We had some success in the pediatrics, and as was mentioned by Dr. Ortega in the next question, we will continue. This is not a static field. It's not a static element for GSK. We will continue with studies. We will continue to work with the agency to bring additional data into these subgroups.

DR. SWENSON: Ms. Bell-Perkins?

MS. BELL-PERKINS: Following up on the same question for the sponsor. I understand that you were disappointed in results for adolescents and African-Americans, but I am assuming there is already knowledge that non-whites, specifically Puerto Rican descent, black, black non-Hispanic are the three top adults, severe sufferers of asthma that have threefold more hospitalization and ER and higher mortality and morbidity.

So what in the structure of your recruiting attended to -- since I would assume you already knew that that was a population that had more of a need than all the other populations, was there a structure in the study? Are you able to change the

structure of how you recruit regionally? Because this has been like this for decades. This is not a new asthma suffering --

MR. YANCEY: So your last point is, I think, actually incredibly relevant to this. It has been this way for decades. There is a challenge to enroll African-Americans, for example. We have been making strides toward moving and trying to find additional African-Americans, and I actually would look back at the data that were actually enrolled.

We are actually overrepresented by the African-American population relative to the CDC statistics. So in the U.S., the African-American population relative to the total is about 18 percent. Our U.S. enrollment of African-Americans was 25 percent.

Now, we have a lower level of overall U.S. recruitment, which was around 12 percent for the global program. The U.S. sites were slow to enroll for this particular study. So there were elements that we were trying to reach, and we will continue

with that.

I think the element around adolescents is one that is a little bit easier to understand. I'm responsible for myself, but when I was an adolescent, it was up to my parents to make sure wherever I traveled, I made it there, and my schedule was at the whim of my parents.

So enrolling adolescents is very challenging, and it has been -- like you said, again, it has been that way for a number of years. So we do take efforts to try to do that, and we have seen that number steadily increase over time.

So there are gains that are being made in both the adolescent and African-American subgroups in terms of their representation into an overall ITT group. But again, the principle of this study was to enroll a population. It wasn't to break down the populations.

We are trying to inform on that. These are very relevant questions. We take it seriously. The FDA has taken it seriously and asked you to consider that. And I hope what we have been able

to show you is the fact that despite the fact that there is low representation, there is not evidence to suggest that their response to the treatment has been different from the overall populations.

So there is some comfort that can be taken in that respect, and we will continue to take all measures possible to continue to increase enrollment of particularly vulnerable groups such as children and more at-risk groups such as African-Americans.

DR. SWENSON: Dr. Blake?

DR. BLAKE: I think I read in the sponsor's briefing document that in the study 997, where there was a year between the end of the primary study and the open label; is that right? There was no rebound effect in terms of higher numbers of exacerbations compared to baseline; is that right? It was just a return kind of to their status quo.

I'm thinking of the people who may start the drug, that their insurance changes. They can't get it for a few months. What would happen to them?

MR. YANCEY: No. There is probably one

really good study that helps inform this, and it was part of the study that was groundbreaking from the Leicester Group and Dr. Pavord's group. So I'd like to bring up a particular slide that looks at exactly what happens to patients when they terminate treatment. So as we're waiting for that slide to build into the screen, let me set the setting first.

In that study, which was presented, there were 60 patients who were treated on either placebo or mepolizumab for 1 year, so it's split in half, so 30 patients on mepolizumab. The group then followed that cohort for the next 12 months.

If I could have the slide up, please? What you are able to see here, firstly, is the blood eosinophil count. And I'm going to move to the right panel because I think it's more germane to the conversation we have been having today.

What is shown in the orange, at least on my screen, are the pre-study means of eosinophils, and you can see that this group is around a count of 300 cells per microliter.

While they were still on study, you can see it says study mean, they had a very rapid and persistent drop in eosinophils that was maintained over the year. What is then shown beyond that period is the follow-up period, and you can see where the first data points that is shown on this particular slide is at 3 months after the end of study. You can see that the eosinophil level begins to return.

What's most reassuring is you see that the eosinophil level just goes back to the pre-baseline level, and then it's maintained over time.

Your other question was around rebound or worsening of symptoms. And if I could have the follow-up slide to this particular slide set.

This is looking at the exacerbation frequency. So what you can see, it's the same setup in this particular slide, you can see that this group of patients -- I want to look at the mepolizumab group in particular here. You can see the exacerbation frequency per quarter. So this is represented per quarter now and not per year.

You can see that there was a drop, as we have been able to show, a 50 percent drop, and Dr. Pavord reported that in this group it's about a 43 percent overall drop in that particular study. And then what you can see is as tracks with the PD effect of eosinophils that I showed you on the last slide, blood eosinophils, you see that exacerbations begin to return.

But perhaps what is most notable on this slide is the fact that the exacerbations do not exceed the pre-study area. So there's actually very clear evidence that there is not rebound of the PD effect, there is not rebound, but patients slowly return.

It was part of the discussion we had earlier. It doesn't appear, at least with the data that's available today, that the drug is disease modifying, but it is controlling the severe asthma that otherwise most of these patients have no other opportunities.

DR. SWENSON: At this point, before we move to the vote, I thought that I would at least try to

wrap up some general points of possible agreement and still remaining questions from this discussion.

First, I think the efficacy for mepolizumab for exacerbation reduction and in the reduction of oral corticosteroid use is quite robust in the study population that we were presented. I don't think there are concerns about the validity of the data to the group.

But we, unfortunately, still have the questions remaining for those of African-American heritage and in the adolescent group simply by virtue of low numbers, despite efforts to try to enrich the population. And going forward, I think it will be just the mandate to all of us that these patients need to be recruited more heavily and brought in to numbers equivalent to their proportional representation.

The other point that was raised, and I think we have fairly good agreement about the level of eosinophilia, the intake of 150 or greater, again seem to be quite predictive for benefits in reduction of both exacerbation rates and steroid

use.

But questions still remain about historical values and whether a single value at any time will be important, or the intake I think has to be something that the agency and the sponsor will struggle with in terms of how this ultimately will be labeled. And I don't think we'll be able to have any more data here. It will have to be just some reasonable discussion and measured thinking about that.

The question about reduction rates for exacerbations in terms of benefit to patients, I don't think we had an answer, but I would surmise that perhaps the quality of life indices that were presented might be heavily dominated by the impacts of having an exacerbation.

I think disruption of life in general with having to drop everything to go to the emergency room or to be hospitalized are probably big, big factors for quality of life measures, although we didn't have a breakdown on those issues.

I believe those are probably the best

synthesis I think we can take from this discussion for the agency, and if there are any other questions you might have of us, I think we should go ahead and proceed to the vote.

(No response.)

DR. SWENSON: Then we will begin to vote. We will be using an electronic voting system. Once we begin the vote, the buttons will start flashing on your microphones, and you need to press very firmly the button, either yes or no or abstain, as you wish.

After everyone has completed their vote, the vote will be locked in, and then the vote will be displayed on the screen, hopefully not within more than about a minute or so. I think the system is pretty good. Then Dr. Toliver will read the vote from the screen into the record.

Then we'll go around the room and ask each individual why they voted and they have another chance to give some emphasis to their vote, and we will continue around the room until we have everyone voted.

So I think if there are no other questions -- the voting questions there then are, do the efficacy data provide substantial evidence of a clinical meaningful benefit for mepolizumab 100 milligrams given subcutaneously once every 4 weeks for the treatment of severe asthma, A, in adults 18 years of age and older; and, if not, what further data should be obtained; and then B, in children 12 to 17 years of age; and, if not, what further data should be obtained?

So this will be the vote on efficacy. So we will vote on 2A, and then we will vote on 2B, and we will go around the room after each vote to discuss why we voted.

So the question then will be 2A, in adults 18 years of age or older, do the efficacy data support evidence of benefit?

(Voting.)

DR. SWENSON: We had a unanimous yes vote on this. Let's begin with Dr. Raghu.

DR. RAGHU: Well, the efficacy data, as has been discussed, is clearly robust, and also there

is no argument about it. The further data that I would like to have seen is a little bit more on the open-label data on the corticosteroid reduction, as well as the eosinophils, et cetera. But on the other hand, the primary endpoint is well met, and I had no problems with accepting the efficacy data.

DR. SWENSON: Dr. Dykewicz?

DR. DYKEWICZ: I do think that the evidence is compelling for the endpoints, both of reduction of exacerbations and also for the reduction in need for oral corticosteroids. And on that last endpoint, I can't overemphasize the importance of that, the ability to reduce oral corticosteroid doses with their potential toxicity in patients with very severe asthma.

DR. TOLIVER: Before you go, I just want to officially read the vote into the record. There are 14 yes votes, zero no votes, zero abstentions, and zero no votes.

DR. SWENSON: Dr. Evans?

DR. EVANS: The endpoints are important and they are robustly achieved.

DR. SWENSON: Ms. Schwartzott?

MS. SCHWARTZOTT: I felt that the data showed plenty of evidence that this would be a meaningful benefit of using this medication.

DR. SWENSON: Ms. Bell-Perkins?

MS. BELL-PERKINS: I'm sure, like the experts at the table, it's pretty clear that the data supports use and the important reduction -- in other drugs have such bad side effects. This could be, even for a small amount, a really important piece to improving quality of life for this subset.

DR. SWENSON: Dr. Au?

DR. AU: I agree with what my colleagues said. I don't have anything else to add.

DR. SWENSON: Dr. Follmann?

DR. FOLLMANN: I voted yes. I don't really have anything to add. I thought the data was quite strong.

DR. SWENSON: Dr. Stone?

DR. STONE: Kelly Stone. I voted yes. The efficacy data was robust for adults in this subpopulation of patients.

DR. SWENSON: Dr. Georas?

DR. GEORAS: I think the efficacy data is strong. I would encourage you to think about the value of the historical eosinophil count as you create the indication. Thank you.

DR. SWENSON: Dr. Swenson. My vote was yes, and I thought it was a robust finding and support that approval.

DR. MORRATO: Elaine Morrato, and I voted yes for the reasons mentioned. I just want to add that maybe thinking forward, part of the challenge of having such a low number of subgroup of African-Americans is the result of these kinds of global development programs.

So FDA might want to consider moving forward establishing a minimum number in a sub-sample of important subgroups that could be worked toward as opposed to leaving it by chance of enrollment.

DR. SWENSON: Dr. Connett?

DR. CONNETT: John Connett. I voted yes. The data seem very consistent and unambiguous for this age group, and I didn't have any doubts about

it.

Are we not having public input on this?

DR. SWENSON: There was no sign-up for any public comment. We had it open. And we do have a patient rep on the panel here.

Dr. Blake?

DR. BLAKE: I voted yes for the reasons that I've heard everybody else say.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: Paula Carvalho. I voted yes for the reasons my colleagues have mentioned. And also, we have to be very aware that this agent as a steroid-sparing medication is highly important.

DR. SWENSON: All right. We will then move to the second part of this question, and that is, do the efficacy data provide substantial evidence of a clinical meaningful benefit given once every 4 weeks for the treatment of severe asthma, in this case, in children or adolescents aged 12 to 17 years of age; and, if not, what further data should be obtained?

So again, the voting procedure will be that

everyone casts their vote, press the button firmly for a reasonable amount of time, and then we'll wait for the results.

(Voting.)

DR. TOLIVER: The vote is as follows: 5 yes votes, 9 no votes, zero abstentions, zero no votes.

DR. SWENSON: And we'll start in the other direction then, this time with Dr. Carvalho.

DR. CARVALHO: I voted no. There was one child in study 97, 25 children in study 88, and Dr. Ortega mentioned two additional ones in study 75. That's a total of 28 kids. Of these, only 16 saw the medication. So I think I'm reluctant to vote yes on that small sample size. This should be studied.

DR. SWENSON: Dr. Blake?

DR. BLAKE: So I voted no because I didn't think there was substantial evidence shown in the trials that they were in, and I'm just uncomfortable recommending for approval of a new class of drug in kids when the data is not really more clear. But I definitely think it should be

pursued for children, for adolescents.

DR. SWENSON: Dr. Connett?

DR. CONNETT: I voted no based partly on what I interpret the company to say, that they intend to study the age groups and African-Americans more carefully.

DR. SWENSON: Dr. Morrato?

DR. MORRATO: Elaine Morrato, and I voted no for the reasons that have been stated. For me, given the paucity of data in adolescents, I didn't feel that the data met the threshold of substantial evidence, especially considering that this might be a drug that is potentially lifelong for children. But I would agree that it certainly warrants further study.

DR. SWENSON: Dr. Swenson. I had a tough one on this one, but I voted yes. I think that there was enough benefit evidenced here to support it. I don't see any compelling reason to think that the age group of 12 to 17 would be so radically different from what they will be five to six or seven years later in their life, that they

should be held back from a possible benefit.

DR. GEORAS: I voted yes, and I would concur with Dr. Swenson's points, and also just say in this severe rare subset of adolescents who suffer from severe asthma, I think we need alternative agents besides continued use of glucocorticoids, and I think this would be one of them.

DR. SWENSON: For the record, that was Dr. Georas. Dr. Stone?

DR. STONE: Kelly Stone. I voted no, really because I answered the question that was asked. Having said that, I am encouraged that there are ongoing studies, and I agree with the comments that I do hope this is available for that age group. There aren't really good options at this point.

DR. SWENSON: Dr. Follmann?

DR. FOLLMANN: I'm Dean Follmann. I voted yes. This was a hard one for me, also. In reading the materials, I was leaning against voting for children, but in my discussions today and so on, I thought where is the evidence they get a different benefit from the rest of the population. I didn't

see evidence of that. I also was uncomfortable sort of denying them this therapy. And so at the end I voted yes.

DR. SWENSON: Dr. Au?

DR. AU: I voted no. Although the results I think are promising, I agree that I just think it's too underpowered to really address any statement of true efficacy.

DR. SWENSON: Ms. Bell-Perkins?

MS. BELL-PERKINS: I voted yes, even though I do agree that we don't have enough data, but there is a real need for a small group of adolescents who are dealing with uncontrollable asthma.

DR. SWENSON: Ms. Schwartzott?

MS. SCHWARTZOTT: I voted no, although I was very torn. My major concern is the lack of data, especially considering that it's a lifelong therapy, and I just erred on the side of caution.

DR. SWENSON: Dr. Evans?

DR. EVANS: I voted no. I certainly concur with the notion that there is a tremendous need for

glucocorticoid-sparing agents, but the data isn't even evaluable, in my mind. So I think that we're stuck for right now.

DR. SWENSON: Dr. Dykewicz?

DR. DYKEWICZ: I, with mixed emotions, voted yes. My thoughts were the following: one, was true the numbers of adolescent patients is relatively low. Would I like to see a larger number of adolescent patients studied, potentially postmarketing, to assure benefit? Yes.

But as a clinician, we really are faced with the issue that in 2015, there are adolescent patients out there with eosinophilic asthma who don't respond to current therapies, including -- maybe they're not eligible for anti-IgE because they don't have allergic disease, but they still have eosinophils, or they've tried that and they have not responded. And in some of these adolescents, they're on corticosteroids.

I think there is enough evidence for me to say if I had an adolescent patient in my clinic who had severe persistent asthma that was of

eosinophilic character and I needed an option to reduce oral corticosteroid use, I'd want to have this drug available.

DR. SWENSON: Dr. Raghu?

DR. RAGHU: I said no primarily going by objective evidence, as has been discussed by others, as well. The underpower of the drug to 17 is real, but on the other hand, there is an unmet need in this adolescent patient population, and I urge very strongly for the sponsor to undertake this study very quickly in this age patient population who might show benefit. So for those reasons I said no.

DR. SWENSON: Dr. Albrecht, do you have a comment? You're not a voting member.

DR. ALBRECHT: I'm not a voting member, but if I may make a comment. I would align with the comments that have been made for the yes votes, so I don't want to repeat that.

But I would like to add the point that this is a very serious condition for a growing body and growing population, and the importance of being

able to reduce steroids I think is extremely important. And to deprive doctors of prescribing this product under their supervision I think might be a mistake.

So that they don't have to prescribe off-label, could the FDA consider adding this into the labeling with special monitoring provisions for this population? Just a suggestion.

DR. SWENSON: At this point then, before we go into the next broad category of the safety issues, I think it would time to take about a 10-minute break. So let us meet back at 2:45.

(Whereupon, at 2:36 p.m., a recess was taken.)

DR. SWENSON: Welcome back. We'll now move to the next discussion point, and I'll read the question here.

Our charge is to discuss the safety data for mepolizumab 100 milligrams subcutaneously administered once every 4 weeks. And in our discussion, we need to discuss the size of the overall database and the adequacy of safety data in

children 12 to 17 years of age.

So we'll open it up for questions around safety now. And I think we have two voting questions that we'll put up; is that right? Are there two?

All right. So we have no particular questions here. The discussion will be just around the safety data that we've heard.

Dr. Follmann?

DR. FOLLMANN: This is just a comment actually. During the presentation I guess of the sponsor, they mentioned study 06, which was the study done in the '90s in patients with moderate asthma, and I noticed the mean age there was 36.

So there might be more or some 12 to 17-year-olds in that study. There were about 200 people, or more than 200 people, on drug. So it might be worth a look to see if there are adolescents in that database and whether they could be used to augment the safety database that you do have.

DR. SWENSON: Any other questions?

(No response.)

DR. SWENSON: Well, I have a question then on the safety concerns around parasitic infections. I wonder if there -- given that this was a very select patient population that was studied and with all of the safety and all of the excellent care that these patients get, when this drug, if approved, and then moves out into the general population where socioeconomic status and other factors that might be risk factors for parasitic infections, whether there is going to be a danger out there to a greater extent.

I realize and I think that it was at least ascertained that they didn't seem to have evidence of a parasitic infection at the time that they were recruited. But was anything more done to determine that? I think stool samples particularly would be a relatively easy thing to do. Most labs can do that. And should that be possibly an entrance criteria that you have no evidence by some laboratory testing of not having a parasitic infection?

I just worry that the safety around that point might be a greater issue once it is in a larger group, a larger population in general use. Either the agency or the sponsor?

DR. LEADBETTER: Thanks for the question. A couple of additional points from the points I made earlier today.

One is that eosinophils are not completely ablated largely in this population receiving mepolizumab, and there is some evidence to suggest, indeed, that you can mount an eosinophilic response despite treatment with mepolizumab in certain situations.

So we do think that there is good reason to believe that individuals can mount an appropriate immune response to a parasitic infection. Preclinical studies also seemed to indicate that, as well, in terms of, again, preclinical models that suggest even with full ablation using knockout mice, that sort of thing, that they can fight off infections, parasitic infections, vis-à-vis the adaptive immune response.

Then lastly, obviously, this is something that because of its importance and its relevance in this population, it is something we'll be watching very closely in the postmarketing arena to look for evidence of increased reporting of such events.

DR. SWENSON: But you were at least concerned enough about this issue that you at least decided to exclude anybody with a parasitic infection.

DR. LEADBETTER: That was largely because we did not want to have individuals who had eosinophilia for reasons other than their eosinophilic asthma.

DR. SWENSON: Dr. Au?

DR. AU: I guess just in the spirit of the discussion, I think that there is good safety data actually on adults at the dose recommended who are being proposed. And so I think the safety data is encouraging both in terms of -- well, around short-term outcomes.

There is some question in my mind still around what happens after 12 months and longer-term

follow-up, where I don't think we have this complete information.

In terms of commenting on the adolescent age, I really do think -- similar to the issue of efficacy, I don't think that there is good data to support safety either. There is no evidence necessarily that it's more harmful.

But the responsibility I think is actually greater for us in terms of potentially exposing adolescents to treatments that we don't naturally know the long-term consequences of. So I think a principle of do no harm actually is an important concept here.

DR. SWENSON: Dr. Raghu?

DR. RAGHU: The concern about herpes zoster is not a small one to me. There was a significant number of patients in the treatment arm that had herpes zoster, whereas the placebo arm had zero, if I recall the slide that was shown, acknowledging that the placebo arm would have been on a higher dose of prednisone.

Therefore, even taking that into account,

this particular compound somehow seemed to predispose people to have herpes zoster infections or exacerbations of their previous zoster infection. So there may be some need to be paying attention the prophylactic interventions such as immunizations and vaccinations. So that needs to be taken into consideration.

DR. SWENSON: Dr. Georas?

DR. GEORAS: I think the safety profile is very reassuring, but I'd like to restate the concern about cancer, especially if this agent is given long term and to acknowledge once again that the available epidemiologic and preclinical data largely in mouse models is very muddy.

But I think one thing we have learned or as an immunologist, I think we need to be aware of the potential for unintended consequences when we start perturbing the very variable human immune system.

So I guess I would just like to encourage some formal tracking or monitoring of cancer risk, especially as this agent is used long term.

DR. SWENSON: And along those same lines, in

a perfect world, I would have loved to have heard from the sponsor models that really get at the question of malignancy risk. I think that despite the cost and time involved, moving to some animal model and then generating the appropriate antibody for that animal, a mouse for instance, and then challenging those mice with various cancers and showing that, in fact, the institution of this antibody did not adversely affect either the spontaneous rate of tumors or the appearance of faster growth of tumors that were already established.

But I still think the malignancy issue has to be followed very, very closely over the postmarketing period, and I hope the agency will institute enough monitoring of that issue.

Dr. Blake?

DR. BLAKE: I just want to follow-up on what Dr. Raghu said, because I looked at the zoster rates, as well. So I would just like to see that that is followed up on, and maybe see if there are recommendations that patients who are on this drug

get vaccinated for herpes zoster, and to look at whether or not the prevalence occurs in a younger population when they're on this drug compared to the average population to see if there is any increased risk for earlier events of zoster if they're on the drug.

DR. SWENSON: There being no further questions, let us proceed to -- I will summarize then.

I think the points that we have heard here are that, given the data that we have seen, there are no obvious safety concerns that have arisen, but that given the limited period of time the drug has been applied, that there may still be concerns about cancers in the long run after many, many years of use. And perhaps even that might extend to opportunistic infections, as well.

But in a global sense, the safety data looked fairly good from what we saw. And we should go ahead and proceed to the voting now, if we could have those questions. Again, as we did with the efficacy data, we're going to vote in two blocks.

One would be the safety data for adults 18 years of age or older and then separately for children aged 12 to 17 years of age.

So we will begin with the voting on 4A. That's the safety of mepolizumab at the dose of 100 milligrams in adults 18 years of age or older. And if you have safety concerns, what further data would be obtained?

So we will begin with the voting. And remember, just hold the button long enough so that your vote will be registered.

(Voting.)

DR. TOLIVER: The vote is as follows: 13 yes votes, 1 no vote, zero abstentions, zero no votes.

DR. SWENSON: All right. We'll begin then with Dr. Raghu, and your vote and reasons.

DR. RAGHU: There was no question in my mind as far as the safety is concerned, and so I said yes.

DR. DYKEWICZ: I don't think that the -- I voted yes. Mark Dykewicz. Although there was the increased signal about the herpes zoster, as has

been pointed out by FDA officials, this is in a population that's also getting corticosteroids, which could be the more probable explanation for this. There are no other signals that would indicate an increased risk for infection, so that's why I voted yes.

DR. SWENSON: Dr. Evans?

DR. EVANS: I voted yes. I think the safety profile looks generally very good. We have identified some areas for postmarketing surveillance that would be important, but in general, I think it looks very good.

DR. SWENSON: Ms. Schwartzott?

MS. SCHWARTZOTT: I voted yes. I also think there should be some postmarket study, but everything else to me looks good.

DR. SWENSON: Ms. Bell-Perkins?

MS. BELL-PERKINS: I voted yes and agree that there should be some postmarket surveillance for long-term use as far as possible malignancies.

DR. AU: This is David Au. I voted yes. I thought that the data on safety was quite strong.

I actually strongly think that there needs to be postmarketing surveillance of long-term outcomes. I think the overall exposure period is relatively short given the duration that this drug is likely to be administered. So we actually don't really know what the long-term consequences are, if any.

DR. SWENSON: Dr. Follmann?

DR. FOLLMANN: This is Dean Follmann. I voted yes. I thought the safety database was pretty strong and compelling.

DR. SWENSON: Dr. Stone?

DR. STONE: Kelly Stone. I voted yes. I agree with the comments about postmarketing surveillance, though.

DR. SWENSON: Dr. Georas?

DR. GEORAS: Steve Georas. I voted yes. I have nothing else to add.

DR. SWENSON: I voted yes. And everything I would mention has already been.

Dr. Morrato?

DR. MORRATO: Elaine Morrato, and I voted yes. I just wanted to add I thought it was

important that the safety profile that was shown with the subcutaneous form was similar to the profile across all of the doses, a tenfold dose range. I thought that was notable.

I think it's also important to remember that even though it's a robust sample of around 1500 patients all studies, this is still not powered to detect the rare events, so things less than 1 percent. Pharmacovigilance is standard, but I would expect that they would have more active study for some of the risks that were considered.

Related to the long-term use issue will also be long-term adherence. We are assuming part of the premise is that people aren't complying with regular therapy and there's 50 percent adherence rates, et cetera. This is a product that's going to require monthly visits to the practitioner in order to get their dose, et cetera.

So will the long-term adherence with the drug be similar to what you see in drugs that are taken by patients at home? That remains to be seen, and another reason to be doing the long-term

follow-up or vigilance is to find out what the adherence rate is and whether or not that's affecting efficacy, as well.

DR. SWENSON: Dr. Connett?

DR. CONNETT: Well, I'm feeling lonely. I voted no, and the reasons were that these were short-term studies, yet this is going to be a lifetime drug, it looks like. If you smoke cigarettes for 32 weeks, you probably wouldn't increase your risk of lung cancer by a perceptible amount.

So I don't think it has been demonstrated, as it says here, that it's safe. I don't see any evidence that it's not, but I don't think it's been absolutely shown.

DR. SWENSON: Dr. Blake?

DR. BLAKE: I voted yes for the reasons that others have already stated.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: I also voted yes, and I also completely agree with postmarketing follow-up and to be very stringent with that, and, also,

appropriate vaccinations to be considered for all these patients.

DR. SWENSON: Okay. We then will move to the second part of this question, and that is the safety issues for the drug in children aged 12 to 17 years of age. Remember to hold the button down, and then we'll take your reasons for your vote.

(Voting.)

DR. TOLIVER: The vote is as follows: 2 yeses, 12 nos, zero abstentions, zero no votes.

DR. SWENSON: Dr. Carvalho, will you lead off?

DR. CARVALHO: I voted no for the reasons that I previously stated, that there are not enough children that were studied. And if the studies are ongoing, which they certainly should be, then I would also recommend that we bring down the age group so that additional children could be studied.

DR. BLAKE: I also voted no primarily for the same reason I voted no against the efficacy, just because there is just not enough data for kids who could be on this for many, many years.

DR. SWENSON: Dr. Connett?

DR. CONNETT: I voted no pretty much for reasons I stated before, but there just hasn't been enough patients in this age group and not enough follow-up.

DR. SWENSON: Dr. Morrato?

DR. MORRATO: Elaine Morrato, and I voted no. For me, less than 20 patients studied on a drug is insufficient to conclude that there is substantial evidence.

I do want to add, though, given the comments that went around on efficacy, that I believe a lack of an approved indication in children doesn't necessarily preclude physicians from prescribing it in children, albeit off-label, that the labeling doesn't regulate medical practice.

It may make it difficult for insurance coverage and affordability, et cetera, but if it's approved for the adult, it doesn't prelude use in children if some doctors see one.

DR. SWENSON: Dr. Swenson. I voted yes. It's a tough one, but I don't see that this

particular age group should be so radically different from the ages that they will be shortly in their own lives to vote yes in one direction and no in the other. So to be consistent, I voted yes. But it's certainly an area that hopefully will have some follow-on data to help.

DR. GEORAS: Steve Georas. I also voted yes and largely for the same reasons as Dr. Swenson.

DR. SWENSON: Dr. Stone?

DR. STONE: Kelly Stone. I voted no. There was no concerning safety signal, but it really is a matter of size of the database.

DR. SWENSON: Dr. Follmann?

DR. FOLLMANN: This is Dean Follmann. I voted no, which is different than my vote on efficacy, and I wanted to explain that a little. There are a couple of reasons.

One is that, statistically, I think looking at the rate ratio, which we did for efficacy, is a little more reliable than just looking for yes/no whether some event has occurred.

I'm also sort of fundamentally a little less

comfortable lumping and combining different groups for safety, which is different than what I feel about with efficacy. Then, it's a small number, but importantly, with children, they'll be on it for a very long time, and somehow I was thinking efficacy we measure in the short-term. We got that down okay. But the safety concern could be manifest years or decades later.

DR. SWENSON: Dr. Au?

DR. AU: This is David Au. I voted no. I agree with the comments that have been made in the no camp. The one thing I'd like to add, though, is that I don't think that adolescents are small adults and that the lungs continue to mature over time, and we don't actually fully mature our lungs until close to the age of 30 or above. So for those reasons, I voted no.

DR. SWENSON: Ms. Bell-Perkins?

MS. BELL-PERKINS: I voted no. Same reasons that couple other folks had voted yes on efficacy and no on safety. There is a difference physiologically, and we don't know if it's going to

be a lifetime of taking this drug, and we just need some more data.

DR. SWENSON: Ms. Schwartzott?

MS. SCHWARTZOTT: I voted no for most of the same reasons. With the further study and whether or not it passes, I think there should be extra strict monitoring criteria, especially for children and adolescents.

DR. SWENSON: Dr. Evans?

DR. EVANS: I voted no, as I did for the efficacy question and for the same reasons, that we lack sufficient data to make that judgment.

DR. SWENSON: Dr. Dykewicz?

DR. DYKEWICZ: This was a tough one. I voted no for this, whereas I had voted yes in the adolescent group in terms of efficacy. I think on the fence, one of the things that made me vote no is when you're looking for safety signals versus efficacy signals, you need larger nths [ph], especially if something would have an occurrence of a couple percentage points, having more than a couple dozen patients would be necessary to

demonstrate that.

On the other hand, tempering all that is the fact that if we're looking at what adolescents may be more vulnerable in terms of side effects that I could conceive of, you could think of, of course, the model of corticosteroids being used in this group causing growth retardation, causing hormonal derangement. I don't see anything about the mechanism of this agent that would raise those types of concerns.

The other members of the panel have also brought up the idea that adolescents placed on this drug would be on lifelong or long-term therapy. I'm not sure that that's the case. Oftentimes, if you look at adolescents, there will be improvement in their asthma, not necessarily that they outgrow it. But to say that an adolescent patient at age 14 gets placed on a drug and is going to be on it for decades, I don't necessarily think that's going to likely happen either.

If nothing else, you are going to be facing the adolescents who want to get off of an agent and

don't want to be compliant with it if they are otherwise doing pretty well.

So again, I'm on the fence about this. I don't see any safety signals, but I would certainly like to see some more patients.

The question would be whether -- looking at the next question, with approval or not, whether there could be the approval of the agent for adolescents with the requirement for postmarketing surveillance. Those are my comments.

DR. SWENSON: Dr. Raghu?

DR. RAGHU: I said no for the same reason I said no for the efficacy, because of the underpower, a small number patient population. And I was very objective and didn't want to extrapolate it to this patient population.

DR. SWENSON: At this point then, we can move to the last question. Now, this is a combined analysis. Do the available efficacy and safety data support approval of mepolizumab at 100 milligrams subcutaneously administered once every 4 weeks for the treatment of patients with severe

asthma.

We'll vote in turn on adults 18 years of age or older, and if you vote no, what further data should be obtained and then we'll move to the children.

So we will vote now on question 5A, that is the combined efficacy and safety data in adults 18 years of age or older.

(Voting.)

DR. TOLIVER: The vote is 14 yeses, zero nos, zero abstentions, zero no votes.

DR. SWENSON: We'll start then with Dr. Raghu.

DR. RAGHU: I said yes for the obvious reasons, which were safety and efficacy has been established.

DR. SWENSON: Dr. Dykewicz?

DR. DYKEWICZ: I think based on our prior questions, the evidence is clear that you've got good benefit with no safety signal. Risk/benefit ratio is excellent.

DR. SWENSON: Dr. Evans?

DR. EVANS: I voted yes for the reasons I voted yes in the previous two. Thank you.

DR. SWENSON: Ms. Schwartzott?

MS. SCHWARTZOTT: I voted yes just for the same reasons as the other questions.

DR. SWENSON: Ms. Bell-Perkins?

MS. BELL-PERKINS: I voted yes for reasons already stated.

DR. SWENSON: Dr. Au?

DR. AU: David Au. I voted yes, same thing.

DR. SWENSON: Dr. Follmann?

DR. FOLLMANN: I voted yes, same thing.

DR. SWENSON: Dr. Stone?

DR. STONE: Kelly Stone. I voted yes. Both efficacy and safety were adequately demonstrated for this subpopulation of patients.

DR. SWENSON: Dr. Georas?

DR. GEORAS: Steve Georas. I voted yes for the same reasons. I'd like to commend the panel and the group for an excellent discussion today. And just to digress for a moment and say I think it's actually really exciting to be able to now

target a cell that we've known for 100 years to be associated with asthma, and I think this is a real step forward in our treatment of this disease.

DR. SWENSON: Dr. Swenson. I voted yes and for all the reasons that have been stated.

Dr. Morrato?

DR. MORRATO: Elaine Morrato, and I voted yes, as well. I agree that this is really exciting data, an exciting benefit in a difficult to treat patient group with high medical need. Because the FDA has asked for information and ideas around appropriate use, I'm going to take a little bit of time and kind of share that with you.

So I'm framing this from consideration of how do we operationalize selection criteria, a screening program in real-world practice. And I went to the WHO site, and they have general guidance for population-based screening programs in general. So I looked through that and have some thoughts based on if you had to apply principles.

So the first principle they say is that the objectives of the screening should be defined at

the outset. I think that has been well established today. There is clear medical need, there is a biological basis for the screening of eosinophils, and there is strong efficacy that's demonstrated when the screening approach has been applied.

The second criteria they mention is there should be a defined target population and scientific evidence of screening effectiveness, and this is where I think you get into the discussion of is it a baseline eosinophil, is it a historical value, et cetera.

I would say yes on the baseline given the modeling and the prospective confirmation in the trials. I still feel it's unclear in terms of a historical value. But I'm not going to fixate on those numbers, and it sounds like FDA and the sponsor will be working that out in their label discussions.

Now, these other ones are around the practical piece of it. So the program should promote equity and access to screening for the entire target population, and I feel that there's

still some outstanding information to answer that that we didn't have today.

I know CBCs are common, and I know certain countries, particularly the UK, have great EHR records that share information across sites. We don't have that consistently here in the U.S.

So I'm worried about, A, how many are having CBCs and, B, does the prescribing physician have access to that information to make their judgment.

I think this can be addressed not so difficulty. It sounds like the sponsor has done some large claims-based data analyses. One you can look at is the CPT codes on the frequency of CBCs that are being drawn, how often. That would give you some sense of at least has it been assessed and how often in the patient.

The other way to really know if it's accessible for the physician would be you can do an EHR health services study and see, in a health system, in their EHR, how easily accessible it is. I would imagine that the company has access to that via their commercial activities.

The question I had is based on the trial data. When I know that 31 percent, even among sites that are selected because of their ability to run trials -- so presumably they're doing pretty good data collection, 31 percent did not have historical records. So it makes me wonder as to what is the real-world gap here.

Another point is that the overall benefits of screening should outweigh the harm. There is not necessarily extra harm here. It's not so much the safety, which is likely minimal, but the harm is potentially lost opportunity of thinking that you are treating someone where there will be an effect and when there is not.

So the question is, well, how long are they going to be on therapy before it is decided it is not working, but that's not unique to this drug.

The harm, which is maybe outside of the purview of FDA, is the cost to society of using a drug that may not efficiently being targeted properly, antibody drug as well as the monthly injection. So it's not just dollars cost, but lost

time and cost for the patient.

So these are some things to think about. And having sat on the Drug Safety and Risk Management Advisory Committee, in which we're always talking about REMS and that, a lot of these issues appear in REMS, how do you ensure that appropriate use in clinical practice plays out the way you saw in the trial.

I'm not saying a REMS is here, but it there are some general principles as to maybe an appropriate use management plan that could be discussed with the sponsor in addition to their pharmacovigilance. And here is where I think the commercialization plans are particularly critical.

So I would agree with the sponsor that labeling guidance is necessary, but it's certainly not sufficient in ensuring good implementation in practice. So what are the wrap-around programs that the company is planning on doing in terms of education and what are their plans to track appropriate use?

I think evaluation of appropriate use could

be an endpoint that's incorporated into pharmacovigilance reporting. And good pharmacovigilance practice using secondary data sets, whether they be EHR-based or claims-based, could be designed and could be coupled in with the regular pharmacovigilance case reporting that's coming in to give some assurance that the education and the direction through the labeling is working out.

I actually think it would be a good model and is probably something that the company is going to be wanting to track anyway to see the uptake of the medicine.

So I gave as lot of information, but some things to consider as you finalize the labeling.

DR. SWENSON: Dr. Connett?

DR. CONNETT: John Connett. I need to explain I think. I voted no on the demonstration of safety, but I'm voting yes on this. And I think the reasons there are that this subset of patients are at very high risk from asthma, and there are at somewhat unknown risks I think from the effects of

this drug.

So it seems to be a question of risk/benefit ratio. So I voted yes because the benefit is clear and the benefit affects a life-threatening disease.

The harm is less clear. I would like to see further follow-up, especially with regard to cancer, but we don't have that in hand right now. So it's a known on one side and really an unknown on the other side, so on balance, I voted yes.

DR. SWENSON: Dr. Blake?

DR. BLAKE: I voted yes for the reasons that I said for safety and efficacy, but I do think that long-term pharmacovigilance is important in order to make sure that with this new class of drug that we're not missing anything.

I think we all remember drugs that have with withdrawn from the market after a length of time of being publicly available. And so I just think that that's very important to continue with that.

DR. SWENSON: Dr. Carvalho?

DR. CARVALHO: I echo Dr. Blake's statement. I completely agree with continuing

pharmacovigilance. This might turn out to be an excellent armamentarium weapon for us. And I also want to commend the agency and the sponsor for their very thorough review of the literature.

DR. SWENSON: And we will now turn, then, to the second part of this question, and that is the available efficacy and safety data, do they support approval for the mepolizumab at 100 milligrams subQ administered every 4 weeks for the treatment of patients with severe asthma?

This will be now a vote for children aged 12 to 17 years.

(Voting.)

DR. TOLIVER: The vote is as follows: 4 yeses, 10 nos, zero abstentions, zero no votes.

DR. SWENSON: All right. We'll start then with Dr. Carvalho.

DR. CARVALHO: The sample sizes are too small and the confidence intervals are too large, but I would certainly agree with continuing these studies. And this may turn out to be something we can use in children, as well.

Right now, it would be clinically-driven as to whether the physician will want to use it off label.

DR. SWENSON: Dr. Blake?

DR. BLAKE: I voted no for the reasons that I said before, but I do think that there is a signal that this is a great drug for pediatric patients, as well. It's just I think longer-term follow-up and additional safety data are warranted.

DR. SWENSON: Dr. Connett?

DR. CONNETT: I agree with Dr. Blake.

DR. SWENSON: Dr. Morrato?

DR. MORRATO: Elaine Morrato and I voted no for the exact reasons that have already been stated.

DR. SWENSON: Dr. Swenson. I voted yes. Again, I think that on a risk/benefit analysis here, I think for this particular pediatric age group, the very likely possibility of reductions of oral corticosteroid use and benefits arising from that, as well as the serious disruption of life with exacerbations warrant extension to this group,

as well. But with all of the issues around the smaller numbers of studies and perhaps children of this age behaving a little bit differently with regard to this drug, I think it is going to behoove us to have long-term follow-up date.

DR. GEORAS: This is Steve Georas. I voted yes, and I acknowledge the concerns of fellow committee members voting no. But I asked myself a question, which was if my 16-year-old daughter was a steroid-dependent asthmatic with a history of multiple exacerbations in the previous year, would I want to treat her with this compound, and the answer, in my mind, is a definite yes.

DR. SWENSON: Dr. Stone?

DR. STONE: Kelly Stone. I voted no based on the available data. I am encouraged that studies are ongoing and certainly hope that the data support it and it becomes available for adolescents.

DR. SWENSON: Dr. Follmann?

DR. FOLLMANN: I voted yes on this. Earlier, I felt that efficacy was shown in children

and safety was not so clear. I didn't vote for safety there. But I think on balance, the risk and benefits, and I would rather have the children have this option for treatment than not.

DR. SWENSON: Dr. Au?

DR. AU: This is David Au. I voted no, basically for the reasons that the other people who voted no have already stated.

There is one other point, which is that in this age group, there is the requirement of assent, or at least consent by the parent, and we don't really actually know what the kind of effects are on children over time by having parents impose what they see as their hope upon their children.

DR. SWENSON: Ms. Bell-Perkins?

MS. BELL-PERKINS: I voted no. I'm very disappointed to have to do that because I think that with appropriate adjustments of recruitment, there is no reason why this population can't be -- the adolescent population can't be included in clinical trials.

This has been -- just like women being

introduced into clinical trials in sufficient numbers, we're now dealing with some minority and adolescents. I would like the FDA to provide more guidance, support, whatever they can, to sponsors to make sure that appropriate numbers of children are signed into these very important medications.

DR. SWENSON: Ms. Schwartzott?

MS. SCHWARTZOTT: I voted no, but I strongly encourage further study on the adolescent subgroup with the FDA and the company. The drug shows great promise, but I need further data, especially with safety, to approve.

DR. SWENSON: Dr. Evans?

DR. EVANS: I voted no. Reflecting off what Dr. Georas said, three of my four kids are in this age range. Two of them are asthmatic. I would like this drug to be available. It seems like a good idea, but we have so little data at this point, I don't know that we can back it on either the safety or the efficacy side right now.

DR. SWENSON: Dr. Dykewicz?

DR. DYKEWICZ: I voted yes. It really does

come down to, as you, Dr. Swenson, have summarized, a risk/benefit and also alternative assessment for this drug. The benefits I think are positive. We still have some equivocation about that. But, again, looking at the alternative treatments in this age group with severe asthma in 2015, adolescents who are on oral corticosteroids and having the ability to potentially get them off oral corticosteroids is important.

From a clinician standpoint, there is also the practical issue that if something does not have FDA approval, I may not be able to get that for my patient if it's off label.

I don't know what type of a program GSK may be considering, but for non-clinician members of the committee, the model that may apply here is that with anti-IgE where the sponsoring company has an application process to try to go through all the hoops and hurdles with the pharmacy benefit managers. And you have a listing of criteria that have to be filled out on the form in that case, what the total IgE level is, whether there has been

demonstration of allergy to perennial allergens, what other controllers have been tried.

I sort of see that a similar process is probably in the offing, but if we don't have formal approval for using this drug in the adolescents, I don't think I'm going to be able to get it for my patients who need it.

DR. SWENSON: Dr. Raghu?

DR. RAGHU: I said no because I have made clear I like to be objective and set aside emotions and personal sentiments about families and such. I like to be a clinician scientist and believe in evidence, so I said no.

It requires evidence to be gained, and I urge very strongly the sponsor to undertake the study very quickly, immediately. Everything is there, so it needs to be done. That's why I said no.

DR. SWENSON: Well, at this point then, before we adjourn, I'd like to ask the agency to give their final thoughts.

DR. GILBERT-McCLAIN: Sure. Thank you,

Dr. Swenson. First, I'd like to thank the committee. I think we've had a very good discussion around the table. And I think that you have addressed all the issues that we've brought before you, and you've given us quite a bit of food for thought that we will take back to further discuss and continue to work through the application, and work with the sponsor as we continue to review the application.

But I think all the issues you brought up have been adequately addressed, and we don't have any further questions. So thank you very much.

Adjournment

DR. SWENSON: So before we adjourn, I would just like to thank everyone involved here, agency, sponsor, panel members. It has been an excellent discussion. I learn something all the time when I'm involved in these things. It's quite educational and fun. Thank you for all of your efforts.

Please, when you leave the room, remember to take all your personal belongings. All the

materials that are left on the table will be disposed of properly, so you can leave any of the briefing documents, as you wish, and they will be recycled.

Again, thank you very much.

(Whereupon, at 3:31 p.m., the meeting was adjourned.)